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THE BURDEN OF STROKE: A GROWING HEALTH CARE AND ECONOMY PROBLEM

MOŽDANI UDAR – RASTUĆI MEDICINSKI I SOCIJALNO EKONOMSKI PROBLEM

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Summary

Stroke is often considered as a significant economy burden in health care systems worldwide. According to epidemiological data, there has been a considerable decrease in stroke morbidity and mortality in most West European countries, mainly because of the implementation of prevention measures. Quite a reverse trend has been observed in most of the Central and East European countries where the epidemic of stroke is expected in the near future. New research facts from the fields of molecular science and genetics have enabled better understanding of the stroke pathogenesis while contemporary neuroimaging techniques as well as Doppler ultrasonography have contributed to our perception of stroke. During the last few years, there has been an increasing demand for redefinition and new classification of stroke and transient ischemic attack, implying new definitions such as acute ischemic cerebral syndromes, or acute neurovascular syndromes. It is important to emphasize the importance of stroke as a medical emergency that should be managed in specialized stroke units. The results from large clinical studies have shown that stroke units significantly reduce the mortality and disability among stroke patients. Treatment of acute ischemic stroke with rTPA-thrombolysis within the first 3 hours from the stroke onset, and antiaggregation and anticoagulation therapy have provided better stroke management. The prevention of risk factors for cardiovascular events is still the most effective measure that can reduce the risk of stroke. New clinical evidence has supported some antihypertensives and statins in stroke prevention due to the additional beneficial effect of the drugs apart from blood pressure and cholesterol lowering. Therefore, it is important to decrease the risk of stroke by implementing primary and secondary prevention, and introducing in practice the recently published recommendations for stroke management.

Key words: *stroke, primary and secondary stroke prevention, stroke units, treatment of stroke, recommendations for stroke management*

Sažetak

Moždani udar je važan zdravstveni i socijalno-ekonomski problem, kako u svijetu tako i u Republici Hrvatskoj. Epidemiološki podaci iz zapadnih zemalja pokazuju smanjivanje pobola i smrtnosti od moždanog udara u posljednjim desetljećima prošloga stoljeća, što je izravna posljedica preventivnih aktivnosti. Međutim, nepovoljan trend porasta učestalosti moždanog udara bilježi se u mnogim državama srednje i istočne Europe, pa se u skoroj budućnosti predviđa prava epidemija obolijevanja od moždanog udara. Nova otkrića u području molekularnih znanosti i genetike pridonose boljem razumijevanju patogeneze moždanog udara, a moderne tehnike slikovnog prikaza mozga i doplerske ultrasonografije svakim danom obogaćuju naše spoznaje o moždanom udaru. Posljednjih godina sve su brojniji prijedlozi da se redefiniraju kriteriji i klasifikacija moždanog udara i prolaznih ishemijskih napadaja, pa se sve više govori o akutnim ishemijskim cerebralnim sindromima (AICS), odnosno o akutnim neurovaskularnim sindromima. Važno je naglasiti da je moždani udar hitno medicinsko stanje koje zahtijeva hitnu zdravstvenu skrb u specijaliziranim jedinicama za liječenje moždanog udara. Rezultati velikih kliničkih ispitivanja pokazali su kako zbrinjavanje bolesnika u jedinicama za liječenje moždanog udara značajno smanjuje smrtnost i invalidnost bolesnika. Trombolitično liječenje primjenom rekombiniranog tkivnog aktivatora plazminogena unutar prva tri sata od nastanka inzulta bitno doprinosi učinkovitom liječenju ishemijskog moždanog udara. Prevencija je i nadalje najučinkovitiji pristup moždanom udaru, jer smanjuje rizik od nastanka moždanog udara djelovanjem na brojne čimbenike rizika. Rezultati velikih kliničkih studija pokazuju da bi novije generacije antihipertenziva i statina mogle imati dodatno povoljno djelovanje u prevenciji moždanog udara. Stoga je nužno potrebno širiti spoznaju o sprječavanju moždanog udara pomoću različitih metoda primarne i sekundarne prevencije, a dosljedno i sveobuhvatno provođenje objavljenih preporuka za zbrinjavanje bolesnika s moždanim udarom može tome značajno doprinijeti.

Ključne riječi: *moždani udar, primarna i sekundarna prevencija moždanog udara, jedinice za liječenje moždanog udara, terapija moždanog udara, preporuke za zbrinjavanje moždanog udara*

Stroke is on the third place of all death causes in the world and the leading cause of death and disability in Croatia. The prevalence of stroke has been on an increase not only in the elderly but also in middle-age population, thus adversely affecting their productivity and quality of life. These aspects contribute to a significant health as well as economy and social burden of stroke. Epidemiological data show a considerable decrease in stroke morbidity and mortality in most West European countries, mainly because of the implementation of prevention measures. The age-specific incidence of major stroke in the Oxford Vascular Study has fallen by 40% over the past 20 years in association with the increased use of preventive treatments and major reductions in premorbid risk factors. On the contrary, there has been a constant increase in the morbidity and mortality of stroke in Croatia. A similar trend has been observed in most Central and East European countries implying an epidemic of stroke in the near future. In the last few years, there has been increasing evidence from most fundamental research studies that have contributed to better understanding of stroke pathogenesis, from the association of ischemic type of stroke and specific genes (gene encoding phosphodiesterase 4D in Island and 5-lypooxigenase protein activation gene), the role of neurotransmitters and excitoxicity of brain tissue damage, the association of hyperhomocysteinemia and stroke, through the role of oxidative stress and angiotensin II in vascular wall damage, which can contribute to stroke.

Modern neuroimaging techniques have significantly contributed to our perception of stroke, thus increasing the demand for redefinition and new classification of stroke and transient ischemic attack (TIA), and indicating new definitions such as acute ischemic cerebral syndromes (AICS) or acute neurovascular syndromes. Noninvasive diagnostic methods for functional and morphological brain imaging like magnetic resonance (MR), computed tomography (CT), single photon emission tomography (SPECT) and positron emission tomography (PET) can provide valuable information on cerebral perfusion patterns and help in assessment of post-stroke brain tissue damage. Doppler ultrasonography has the leading role in the assessment of cerebral blood flow pathology. In addition to extracranial and transcranial Doppler (TCD), methods which allow prompt evaluation of cerebrovascular status and detection of blood vessel pathology, power Doppler, 3D ultrasonography, transcranial color coded sonography (TCCS) and functional TCD have frequently been used in clinical practice. Furthermore, measurement of the intima-media thickness (IMT) of carotid bifurcation and

Moždani udar je i nadalje treći uzrok smrtnosti u svijetu, a prvi uzrok smrtnosti u Republici Hrvatskoj. Uz to, moždani udar je prvi uzrok invalidnosti u nas i u svijetu. Svjedoci smo i činjenice da moždani udar više ne zahvaća samo starije dobne skupine; u zadnje vrijeme od moždanog udara sve češće obolijevaju i bolesnici u najproduktivnijim godinama života. Sve to čini moždani udar velikim zdravstvenim kao i duštvenim i ekonomskim problemom. Epidemiološki podaci iz zapadnih zemalja pokazuju smanjivanje pobola i smrtnosti od moždanog udara u posljednjim desetljećima prošloga stoljeća, što je izravna posljedica preventivnih aktivnosti. Značajan pad incidencije moždanog udara od čak 40% zabilježen je u velikoj populacijskoj studiji, Oxfordshire Community Stroke Project, koja je provedena u Velikoj Britaniji tijekom posljednjih 20 godina. Rezultati studije pokazali su kako primjena mjera prevencije značajno smanjuje predmorbidne rizične čimbenike snižavajući serumski kolesterol i povišen krvni tlak te smanjujući broj pušača uz preventivnu primjenu antiagregacijske terapije i lijekova za snižavanje lipida i hipertenzije. Nasuprot tome, podaci za Hrvatsku pokazuju stalan porast pobola i smrtnosti od moždanog udara. Sličan nepovoljan trend porasta učestalosti moždanog udara bilježi se i u ostalim državama srednje i istočne Europe, kao i u većini zemalja u razvoju, pa se u dolazećim desetljećima predviđa prava epidemija obolijevanja od moždanog udara.

Posljednjih godina svjedoci smo brojnih novih fundamentalnih otkrića o moždanom udaru koja bi se mogla pokazati značajnima u razumijevanju patogeneze moždanog udara: od povezanosti obolijevanja od ishemijskog moždanog udara i prisutnosti određenih gena (npr. povezanosti gena za fosfodiesterazu 4D u Islandu, gen za protein koji aktivira 5-lipooksigenazu) preko uloge neurotransmitera i ekcitotoksičnosti u oštećenju moždanog parenhima, povezanosti hiperhomocisteinemije i moždanog udara, pa sve do uloge oksidativnog stresa i angiotenzina II. u oštećenju stijenka moždanih krvnih žila, čime se stvaraju preduvjeti za nastanak moždanog udara.

Nove metode i tehnike slikovnog prikaza svakim danom obogaćuju spoznaje o moždanom udaru, tako da su posljednjih godina sve brojniji prijedlozi da se redefiniraju kriteriji i klasifikacija prolaznih ishemijskih napadaja (TIA) i moždanog udara, pa se sve više govori o akutnim ishemijskim cerebralnim sindromima (AICS), odnosno o akutnim neurovaskularnim sindromima. Neinvazivne metode za funkcionalni i anatomski prikaz mozga, moždanog krvotoka i metabolizma poput magnetske rezonancije (MR)i kompjutorizirane tomografije (CT), jednofotonske emi-

carotid arteries by means of extracranial Doppler has an important role as an independent factor for stroke prediction. The advantages of Doppler ultrasonography methods are noninvasiveness, low cost, and the possibility of repeat examination at bedside. Doppler diagnostic methods are invaluable tools often used in cerebral blood evaluation in primary stroke prevention as well as in secondary stroke prevention after carotid surgery. At this point, we are able to treat efficiently ischemic stroke with rTPA-thrombolysis, within the first 3 hours from stroke onset. Thrombolysis treatment must be performed according to clinical protocol because any protocol deviation can produce serious adverse events. Although, thrombolysis can only be used in a small number of patients, it is regarded as a guideline to urgent and efficient ischemic stroke treatment. Besides research studies about TCD-enhanced thrombolysis, numerous investigations of penumbra region have been conducted. Unfortunately, the risk of hemorrhage is another serious obstacle in thrombolysis treatment. New clinical evidence show that some enzymes like metalloproteinase might induce secondary hemorrhage after thrombolysis. Preliminary research studies of the use of neuroimaging methods (perfusion MRI and diffusion MRI, PET) might prolong the 3-hour window in a strictly selected group of ischemic stroke patients.

Besides thrombolysis, antiaggregation therapy has an important role in ischemic stroke management. It is recommended not only in acute ischemic stroke treatment but also after TIA and in patients with risk factors for stroke. Anticoagulation therapy is indicated in specific circumstances of acute ischemic stroke and also in secondary prevention of cardiac diseases (atrial fibrillation). In patients with high-grade carotid artery stenosis, endarterectomy is still therapy of choice. Besides classic endarterectomy, there has been an increasing number of carotid artery surgeries performed in local anesthesia, while blood vessel dilatation and stenting are restricted to controlled clinical trials.

Results of large clinical studies have shown that stroke management in specialized stroke units can significantly reduce the mortality and neurologic disability even without thrombolysis treatment.

Therefore, restructuring of health care services is urgent because stroke must be accepted as medical emergency that requires emergency transport to an appropriately equipped medical center where stroke patients can be treated properly. In spite of all this, stroke is associated with high mortality rates. Stroke patients are often disabled by severe neurologic and functional limitations in movesijske tomografije mozga (SPECT) i pozitronske tomografije mozga (PET) pomažu u procjeni cerebrovaskularnih poremećaja te stupnja oštećenja nakon vaskularnog inzulta. U dijagnostici patologije moždane cirkulacije dopler-ska je sonografska dijagnostika postala nezaobilaznom metodom. Osim ekstrakranijskog obojenog doplera i transkranijskog doplera koji omogućuju brzu procjenu cerebrovaskularnog statusa bolesnika te prikaz raznih patoloških stanja na krvnim žilama, sve više se upotrebljavaju osnaženi dopler, trodimenzijski dopler, bojom kodirana transkranijska sonografija i funkcionalni transkranijski dopler. Osim toga, doplerska ultrasonografija omogućuje mjerenje debljine intime i medije (*intima-media thickness*, IMT) karotidnih arterija i karotidne bifurkacije kao značajnog predskazatelja za nastanak moždanog udara. Sve te pretrage su neinvazivne, mogu se ponavljati bez rizika za bolesnika, a pogodne su i za primjenu uz bolesnički krevet. Time su postale glavnom dijagnostičkom metodom kako u primarnoj prevenciji cerebrovaskulamih bolesti, u praćenju promjena moždane cirkulacije, tako i u sekundarnoj prevenciji i u praćenju bolesnika nakon operacijskih zahvata.

Prvi put u povijesti na raspolaganju nam stoji učinkovito liječenje ishemijskog moždanog udara otapanjem ugruška, tj. trombolizom uz primjenu rekombiniranog tkivnog aktivatora plazminogena, ali samo unutar prva tri sata od nastanka moždanog udara. Liječenje se provodi po točno određenom protokolu, jer svako odstupanje donosi velik rizik komplikacija. Iako je trombolizu moguće provesti samo u malog broja bolesnika, ona je putokaz da terapija ishemijskog moždanog udara postoji i da treba naglašavati potrebu brze reakcije bolesnika, njegove okoline i medicinskog osoblja. Uz najnovija istraživanja usmjerena ka potpomaganju trombolize pomoću kontinuiranog promatranja transkranijskim doplerom (TCD-om) provode se brojna istraživanja koja imaju za cilj djelovati na penumbru. Nažalost, opasnost od sekundarnih krvarenja dodatno komplicira primjenu trombolitične terapije. Novija istraživanja ukazuju na ulogu metaloproteinaza u nastanku sekundarnih krvarenja nakon trombolize i možda otvaraju nove mogućnosti u povećanju sigurnosti primjene rekombiniranog tkivnog aktivatora plazminogena. Nadalje, preliminarna istraživanja primjene novih, sofisticiranih metoda slikovnog prikaza (npr. perfuzijske i difuzijske tehnike magnetske rezonancije, perfuzijska kompjutorizirana tomografija) pobuđuju nadu u produženje trosatnog terapijskog prozora u određenih, strogo odabranih bolesnika.

U terapiji ishemijskog moždanog udara se uz trombolizu primjenjuje i antiagregacijsko liječenje. Uz terapiju akut-

ment, communication, perception, cognition, and many have neuropsychological deficits like cognitive impairment, post-stroke dementia and post-stroke depression.

Rehabilitation is the key word in post-stroke care. Early rehabilitation might reduce disability and functional system impairment. Although rehabilitation programs do not alter neurologic deficit, they may contribute to the patient's physical independence. Rehabilitation team that comprises multidisciplinary collaboration helps the patients in every day activities including their families.

The best approach to stroke management is prevention. Primary endpoint of stroke prevention is reduction in the risk of stroke by influencing stroke risk factors. The major risk factors for stroke include hypertension, elevated serum lipid levels, myocardial infarction, atrial fibrillation, carotid artery stenosis, diabetes, smoking and alcohol consumption, inappropriate dietary habits and inadequate physical activity.

Recently published data from large, randomized clinical trials show that lowering of blood pressure and elevated cholesterol is associated with a significant decrease in stroke risk. Besides blood pressure and cholesterol lowering it seems that the use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium antagonists (CA) and statins could provide some additional beneficial effects in reducing the risk of stroke. Statins could have a beneficial effect on stabilizing atherosclerotic plaque. In the last few years, stroke management has significantly improved, mainly due to numerous research studies.

Considering new clinical evidence in stroke management, we must recognize stroke as a medical emergency that should be treated at specialized stroke units, emphasizing the need of establishing such units in all major health institutions throughout the country. Recommendations for stroke management could significantly improve stroke care organization and contribute to the reduction of stroke mortality in Croatia.

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nog ishemijskog moždanog udara primjena antiagregacijskih lijekova preporuča se i osobama s čimbenicima rizika, te nakon TIA. Antikoagulantna terapija indicirana je u posebnim slučajevima akutnog ishemijskog moždanog udara, a u sekundarnoj prevenciji nalazi mjesto kod određenih srčanih bolesti (atrijska fibrilacija). Kod simptomatskih bolesnika sa značajnom stenozom karotidnih arterija kirurški zahvat je i nadalje terapija izbora. Uz klasičnu endarterektomiju sve češće se primjenjuje operacijski zahvat na karotidnim arterijama u lokalnoj anesteziji, dok su metode dilatacije arterija i stentinga i dalje ograničene samo na kontrolirana klinička ispitivanja.

Rezultati velikih kliničkih ispitivanja pokazali su kako se zbrinjavanjem bolesnika u primjereno opremljenim odjelima (jedinice za liječenje moždanog udara, *stroke units*) čak i bez primjene trombolize značajno smanjuju smrtnost i invalidnost bolesnika. Stoga je neophodna reorganizacija medicinske službe kako bi se moždani udar shvatio kao hitno stanje koje zahtijeva hitan transport u primjereno opremljenu ustanovu gdje će se bolesnike moći odgovarajuće zbrinuti.

Unatoč značajnom napretku u zbrinjavanju bolesnika s moždanim udarom, moždani udar je i nadalje je povezan sa značajnom smrtnošću. U bolesnika nakon preboljelog moždanog udara vrlo često zaostaju teška neurološka oštećenja i funkcionalna ograničenja u kretanju, komunikaciji, percepciji, spoznaji, a sve više se govori i o psihičkim i neuropsihološkim promjenama nakon preboljelog moždanog udara, od vaskularnih kognitivnih oštećenja do vaskularne demencije i depresije. Rehabilitacija je ključna u zbrinjavanju bolesnika s preboljelim moždanim udarom. Rano započetom rehabilitacijom moguće je dodatno smanjiti invalidnost i oštećenja funkcionalnih sustava. Iako rehabilitacijski programi ne mijenjaju neurološki deficit bolesnika, mogu značajno pridonijeti osamostaljivanju bolesnika. Kvalitetnu rehabilitaciju treba provoditi multidisciplinski tim stručnjaka, a bolesnici i članovi njihovih obitelji moraju biti uključeni u rehabilitacijski proces.

Prevencija je i nadalje najbolji pristup moždanom udaru. Cilj prevencije je smanjiti rizik od nastanka moždanog udara djelovanjem na čimbenike rizika. Najčešći čimbenici rizika uključuju hipertenziju, povišene vrijednosti lipida u serumu, infarkt miokarda, atrijsku fibrilaciju i karotidnu stenozu, šećernu bolest, pušenje i konzumiranje alkohola, neprimjerenu prehranu te smanjenu tjelesnu aktivnost. Rezultati velikih kontroliranih, dvostruko slijepih, placebom kontroliranih studija objavljeni posljednjih godina pokazuju kako bi novije generacije antihipertenziva (npr. inhibitori konvertaze angiotenzina /ACEI/, blokatori

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kalcijevih kanala, blokatori angiotenzinskih receptora) mogli uz djelovanje na snižavanje tlaka imati i dodatne povoljne učinke na smanjivanje rizika od moždanog udara. Tako i za statine postoje neizravni dokazi da bi mogli imati dodatno djelovanje u prevenciji moždanog udara, uz njihovo povoljno djelovanje na snižavanje razine kolesterola, najvjerojatnije djelovanjem na stabiliziranje ateroskleroskih plakova.

Posljednjih godina svjedoci smo značajnog napretka u zbrinjavanju bolesnika s moždanim udarom. Uzimajući u obzir brojna istraživanja koja su u tijeku, za vjerovati je da ćemo u budućnosti biti svjedoci i većih iskoraka.

Nažalost, sve navedene spoznaje još uvijek nisu opće prihvaćene i često se u praksi ne primjenjuju. Stoga je nužno potrebno među zdravstvenim djelatnicima i u pučanstvu širiti spoznaju da se moždani udar može spriječiti dosljednom primjenom različitih metoda primarne i sekundarne prevencije. Također valja stalno naglašavati kako je moždani udar hitno medicinsko stanje koje zahtijeva hitan zdravstveni tretman u primjereno opremljenim jedinicama, tj. jedinicama za liječenja moždanog udara, koje bi trebalo osnovati u svim većim zdravstvenim ustanovama u Republici Hrvatskoj. Dosljedna i sveobuhvatna primjena objavljenih preporuka za zbrinjavanje bolesnika s moždanim udarom može tome značajno doprinijeti.

EPIDEMIOLOGY OF STROKE
EPIDEMIOLOGIJA MOŽDANOG UDARA

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The World Health Organization (WHO) calls attention to the serious fact that more than 16.5 million people in the world and more than 5 million people in Europe die from cardiovascular disease *per* year. The proportion of cerebrovascular diseases in the world and in Europe is 32.9% and 29.4%, respectively. Globally, cerebrovascular diseases are the cause of death in some 5.5 million people, 1.5 million of these in Europe. In 1990, cerebrovascular diseases ranked second, immediately following ischemic heart disease, of the 15 most common causes of death. Projections for 2020 show that these two groups of diseases will continue to be the leading causes of death worldwide. According to the Global Burden of Disease study, expressed as Disability Adjusted Life Years (DALY), cerebrovascular diseases ranked sixth among the 15 leading causes of disease and lesions in the world in 1990. The estimates for 2020 predict these diseases to rank fourth at the global level, immediately after ischemic heart disease, major depression and injuries inflicted in traffic accidents, and second in industrialized countries, immediately following ischemic heart disease.

Epidemiological studies for Europe show great differences in the cardiovascular disease overall mortality rates. The lowest rates are recorded in the countries of West Europe, especially in Mediterranean countries, and highest in the countries of Central and East Europe.

In the group of cardiovascular diseases, the main causes of death are ischemic heart diseases and cerebrovascular diseases. As for ischemic heart diseases, the mortality rates for cerebrovascular diseases are also lowest in the West Europe countries and highest in East Europe countries. The analysis of mortality records from 30 European countries performed by Sans *et al.* has shown the standardized mortality rate of cerebrovascular diseases in men aged 45-74 in the 1990-1992 period to be lowest in Switzerland (54/100,000), France (67/100,000) and Island (75/100,000), and highest in Bulgaria (396/100,000), Russian Federation (409/100,000) and Ukraine (606/100,000). In women, the lowest rates were also recorded in Switzerland (32/100,000), France (35/100,000) and Island (48/100,000),

Svjetska zdravstvena organizacija (SZO) upozorava kako na godinu u svijetu od kardiovaskularnih bolesti umire preko 16,5 milijuna, a u Europi više od 5 milijuna ljudi. Udio cerebrovaskularnih bolesti na razini svijeta iznosi 32,9%, a u Europi 29,4%. Globalno cerebrovaskularne bolesti uzrok su smrti u oko 5,5 milijuna ljudi, a od toga blizu 1,5 milijun u Europi. Cerebrovaskularne bolesti 1990. godine nalazile su se na drugom mjestu iza ishemijskih bolesti srca među 15 najčešćih uzroka smrti, a projekcije za 2020. godinu govore da će ove dvije skupine i dalje biti vodeći uzrok smrti u svijetu. Prema studiji Globalnog opterećenja bolestima izraženo u godinama života s invaliditetom (*disability adjusted life year*, DALY) među 15 vodećih uzroka bolesti i ozljeda u svijetu 1990. godine cerebrovaskularne bolesti bile su svrstane na šesto mjesto. U procjenama za 2020. godinu predviđa da će se na razini svijeta nalaziti na četvrtom mjestu, iza ishemijskih bolesti srca, velike depresije i ozljeda u prometnim nesrećama, a u razvijenim zemljama na drugom mjestu iza ishemijskih bolesti srca.

Epidemiološke analize na razini Europe pokazuju velike razlike u stopama smrtnosti za kardiovaskularne bolesti ukupno. Najniže stope smrtnosti bilježi se u zemljama Zapadne Europe, osobito u mediteranskim zemljama, a najviše su stope smrtnosti od ovih bolesti u zemljama Središnje i Istočne Europe.

Glavni uzroci smrti iz skupine kardiovaskularnih bolesti su ishemijske bolesti srca i cerebrovaskularne bolesti. Kako za ishemijske bolesti srca tako su i za cerebrovaskularne bolesti stope smrtnosti najniže u zemljama Zapadne Europe, a najviše u zemljama Istočne Europe. Prema analizi podataka o smrtnosti iz 30 europskih zemalja Sansa i suradnika, standardizirana stopa smrtnosti od cerebrovaskularnih bolesti za dobnu skupinu od 45-74 godine 1990-1992. godine za muškarce bila je najniža u Švicarskoj (54/100.000), Francuskoj (67/100.000) i Islandu (75/100.000), a najviša u Bugarskoj (396/100.000), Ruskoj Federaciji (409/100.000) i Ukrajini (606/100.000). Za žene najniže stope zabilježene su također u Švicarskoj (32/100.000), Francuskoj (35/100.000) i Islandu (48/100.000), a najviše u Bugarskoj (259/100.000), Ruskoj Federaciji (271/100.000)

and highest in Bulgaria (259/100,000), Russian Federation (271/100,000) and Ukraine (408/100,000). In men, the highest rates were 11-fold lowest rates, whereas in women the highest to lowest rate ratio was as high as 13:1.

However, unlike cardiovascular diseases in total and ischemic heart diseases, the standardized mortality rates of cerebrovascular diseases in Mediterranean countries show quite a wide range. For example, during the 1990-1992 period the rate for men aged 45-74 was 67/100,000 in France and 276/100,000 in Portugal. The respective rates for women were from 35/100,000 and 158/100,000. In all countries, the age specific mortality rates are lower in women than in men, and the mortality pattern is more favorable for the former.

According to the American Heart Association Scientific Statement from 2001, the incidence of ischemic stroke increases from the age of 55 with each decade of life. The incidence is higher in men (174/100,000) than in women (122/100,000), with the overall incidence of 145/100,000.

The same institution summarized the current concepts on the risk factors for ischemic stroke. The nonmodifiable risk factors are age, sex, and family history of stroke or TIA. The modifiable risk factors include hypertension, smoking, diabetes mellitus, asymptomatic carotid stenosis, hyperlipidemias, atrial fibrillation and some other cardiac diseases. Obesity, lack of physical activity, unfavorable dietary habits, alcohol abuse, hyperhomocysteinemia, hypercoagulability, hormone replacement therapy, oral contraceptives and inflammatory processes are considered as yet inadequately documented or potentially modifiable risk factors. It is reported that the annual rate of stroke increases with age and presence of risk factors, thus the expected rate of stroke is as follows:

- age ≤ 65, without risk factors 1.0%
- age ≤ 65, with risk factors 4.9%
- age 65-75, without risk factors 4.3%
- age 65-75, with risk factors 5.7%
- age ≥ 75, without risk factors 3.5%
- age ≥ 75, with risk factors 8.1%

Epidemiologic Survey of Cerebrovascular Diseases in Croatia

The general, specific and age standardized mortality rates in total population and in the 0-64 age group, the rates of hospitalization and of the diseases recorded at general medicine service were used to present the patterns of cerebrovascular disease mortality and morbidity in Croatia.

i Ukrajini (408/100000). Najviše stope u muškaraca bile su 11 puta veće u odnosu na najniže stope, a u žena je omjer najviših stopa u odnosu na najniže bio čak 13:1.

Međutim, za razliku od kardiovaskularnih bolesti ukupno i ishemijskih bolesti srca, standardizirane stope smrtnosti od cerebrovaskularnih bolesti u mediteranskim zemljama pokazuju dosta velik raspon. Primjerice, za muškarce u dobi od 45-74 godine 1990-1992. godine stopa je u Francuskoj iznosila 67, a u Portugalu 276/100.000. Odgovarajuće stope za žene kretale su se od 35 u Francuskoj do 158/100.000 u Portugalu. U svim su zemljama dobno specifične stope smrtnosti niže u žena nego u muškaraca, a i kretanje smrtnosti je povoljnije za žene nego za muškarce.

Prema American Heart Association Scientific Statement iz 2001. godine incidencija ishemijskog moždanog inzulta od 55. godine života udvostručuje se za svako desetljeće života. Incidencija je viša u muškaraca (174/100.000) nego u žena (122/100.000), dok ukupna incidencija iznosi 145/100.000.

Isti izvor sabrao je suvremene spoznaje o čimbenicima rizika za ishemijski moždani inzult. Među čimbenicima na koje se ne može utjecati su dob, spol i inzult ili TIA u obiteljskoj anamnezi. Među čimbenike na koje se može utjecati ubraja hipertenziju, pušenje, šećernu bolest, asimptomatsku stenozu karotide, hiperlipidemije, atrijsku fibrilaciju i još neke srčane bolesti. Pretilost, tjelesnu neaktivnost, nepravilnu prehranu, prekomjerno uzimanje alkohola, hiperhomocisteinemiju, hiperkoagulabilnost, hormonsko nadomjesno liječenje, uzimanje oralnih kontraceptiva i upalne procese ubraja u dosad nedovoljno dokumentirane ili potencijalno izmjenjive čimbenike rizika. Navodi se da godišnja stopa inzulta raste s dobi i prisutnošću rizičnih čimbenika, tako da očekivana godišnja stopa inzulta iznosi:

- do 65 godina, bez čimbenika rizika 1,0%
- do 65 godina, s čimbenicima rizika 4,9%
- 65-75 godina, bez čimbenika rizika 4,3%
- 65-75 godina, s čimbenicima rizika 5,7%
- 75 i više godina, bez čimbenika rizika 3,5%
- 75 i više godina, s čimbenicima rizika 8,1%

Epidemiološki prikaz cerebrovaskularnih bolesti u Hrvatskoj

Za prikaz kretanja smrtnosti i pobola od cerebrovaskularnih bolesti u Hrvatskoj u radu se rabe opće, specifične i dobno standardizirane stope smrtnosti ukupno i za dobnu skupinu od 0-64 godine, te stope hospitalizacije i bolesti registrirane u općoj medicini. U Hrvatskoj su kardiovasku-

In Croatia, cardiovascular diseases are the leading cause of death. In 2003, there were 27,872 deaths due to cardiovascular diseases, accounting for 53.0% of overall mortality. The most common diagnostic subgroups specified as the cause of death are ischemic heart disease (WHO ICD I20-I25) with 33.1% and cerebrovascular diseases (WHO ICD I60-I69) with 31.3%.

It should be emphasized, however, that cerebrovascular diseases ranked second, immediately following ischemic heart disease, among the 10 leading causes of death in 2003 (analyzed according to parameters for the WHO Health for All program), and accounted for 15.9% of overall mortality. Cerebrovascular diseases are the second most common cause of death in both men and women, where they account for 13.2% and 18.7% of overall mortality, respectively. This means that every seventh to eighth man and almost every fifth woman in Croatia die from cerebrovascular disease.

The general rate of cerebrovascular disease mortality rose until 1989, when it was 182.5/100,000, whereafter the rising trend was observed to stop. In 1990, the rate was 181.1/100,000, then stagnating at a lower level between 1991 and 1995 to increase to 184.4/100,000 in 1996. In 1998, the rate was 184.0/100,000 (it should be noted that in this year, the methodology of vital events registration was changed, i.e. persons staying in Croatia for more than one year were also recorded in addition to Croatian citizens). In 2000, the rate was 191.3/100,000, and in 2003 it was 188.4/100,000.

During the 1985-2003 period, the lowest absolute number of deaths from cerebrovascular diseases in Croatia was recorded in 1992, i.e. 7925 or 32.0% of all causes of death from the group of cardiovascular diseases. The highest number of deaths due to cerebrovascular diseases (n=8901) was recorded in 1999, accounting for 32.9% of all deaths from cardiovascular diseases, whereas in 2003 there were 8360 (30.0%) such deaths.

Until 1991, the general mortality rate for cerebrovascular diseases (177.14/100,000) exceeded the mortality rate for ischemic heart diseases (136.43/100,000). An abrupt increase in the diagnostic group of ischemic heart diseases as the cause of death occurred in 1991 (136.43/100,000) and 1992 (182.26/100,000) as compared with 1990 (82.40/100,000). The reason for this was the changed methodology of death cause registration and processing, and since then the mortality rates for ischemic heart diseases have been continuously higher than the mortality rates for cerebrovascular diseases.

Analysis according to age reveals the number of deaths and age specific mortality rates due to cerebrovascular

larne bolesti vodeći uzrok smrti. Godine 2003. zabilježene su 27.872 osobe umrle zbog bolesti srca i krvnih žila, a udio u ukupnoj smrtnosti iznosio je 53,0%. Najčešće dijagnostičke podskupine kao uzrok smrti su ishemijska bolest srca (šifre I20-I25 MKB SZO) s udjelom od 33,1% i cerebrovaskularne bolesti (šifre I60-I69 MKB SZO) s udjelom od 31,3%.

Međutim, treba istaknuti da se među 10 vodećih uzroka smrti u Hrvatskoj 2003. godine (analizirano sukladno pokazateljima za program "Zdravlje za sve" SZO) cerebrovaskularne bolesti nalaze na drugom mjestu, iza ishemijske bolesti srca, a njihov udio u ukupnoj smrtnosti iznosi 15,9%. One se nalaze na drugom mjestu s udjelom od 13,2% odnosno 18,7% u ukupnoj smrtnosti muškaraca i žena. To zapravo znači da svaki sedmi do osmi muškarac i gotovo svaka peta žena u Hrvatskoj umiru od cerebrovaskularne bolesti.

Opća stopa smrtnosti od cerebrovaskularnih bolesti rasla je do 1989. godine, kada je iznosila 182,5/100.000, a potom se zapaža zaustavljanje trenda porasta ovih stopa. Godine 1990. stopa iznosi 181,1/100.000, u razdoblju od 1991. do 1995. oscilira na nešto nižoj razini, 1996. se penje na 184,4, 1998. iznosi 184,0/100.000 (uz napomenu da je te godine došlo do metodoloških promjena registracije vitalnih događaja tako da se uz državljane Hrvatske registriraju i osobe koje u Hrvatskoj borave duže od godinu dana). Godine 2000. stopa iznosi 191,3/100.000, a 2003. godine 188,4/100.000.

U Hrvatskoj je u razdoblju od 1985. do 2003. godine najniži apsolutni broj umrlih od cerebrovaskularnih bolesti zabilježen 1992. godine, a iznosio je 7925 ili 32,0% svih uzroka smrti iz skupine kardiovaskularnih bolesti. Najveći broj umrlih od cerebrovaskularnih bolesti (8901 osoba) zabilježen je 1999. godine s udjelom od 32,9% u ukupnom broju umrlih od kardiovaskularnih bolesti srca, dok je 2003. godine taj broj iznosio 8360, a udio 30,0%.

Opća stopa smrtnosti od cerebrovaskularnih bolesti bila je do 1991. viša (177,14/100.000) nego stopa smrtnosti od ishemijskih bolesti srca (136,43/100.000). Nagliji porast dijagnostičke skupine ishemijskih bolesti srca kao uzroka smrti zabilježen je 1991. (136,43/100.000) i 1992. (182,26/100.000) godine u odnosu na 1990. godinu (82,40/100.000), što je bilo uzrokovano promjenama u registriranju i obradi uzroka smrti, otkada su stope smrtnosti za ishemijske bolesti srca kontinuirano više od stopa smrtnosti za cerebrovaskularne bolesti.

Analiza prema dobi pokazuje kako broj umrlih i dobno specifične stope smrtnosti od cerebrovaskularnih bolesti rastu s dobi, a izrazitiji porast bilježi se poslije 50. godine života. U Hrvatskoj su stope smrtnosti od cerebrovasku-

diseases to increase with age, the increase being more pronounced after the age of 50. In Croatia, the cerebrovascular disease mortality rates are higher in men than in women for all age groups.

Mortality analysis according to sex shows the general mortality rates for cerebrovascular diseases in 2003, likewise previous years, to be higher in women (211.7/100,000) than in men (163.33/100,000), whereas the overall rate was 188.4/100,000. The reason for this was the greater number of deaths among females from older age groups and the considerably higher proportion of elderly women as compared with elderly men, all this resulting in a higher overall mortality rate from cerebrovascular diseases in women.

In Croatia, the most common cause of death as individual diagnosis from the group of cerebrovascular diseases is stroke unspecified as hemorrhage or infarction (WHO ICD X rev., I64). In 2003, this diagnosis accounted for 72.9% of all deaths from cerebrovascular diseases, followed by cerebrovascular disease sequels (I69) with 9.5% and intracerebral hemorrhage (I61) with 8.1%.

For Croatia, the age adjusted mortality rates for from the WHO Health for All program database for 2002 (the latest comparable data available) were as follows: 482.5/100,000 for overall cardiovascular diseases; 159.5/100,000 for ischemic heart disease; and 145.3/100,000 for cerebrovascular diseases. These rates were lower than the average rates for the Central and East Europe countries for overall cardiovascular diseases (526.2/100,000) and ischemic heart disease (184.1/100,000), and slightly higher than the average rates for cerebrovascular diseases (144.7/100,000). However, the Croatian rates exceeded the average rates for Europe as a whole in 2001 (the latest comparable data available) for cardiovascular diseases (469.0/100,000) and cerebrovascular diseases (137.5/100,000), but were lower in case of ischemic heart disease (219.9/100,000).

Considering deaths due to cerebrovascular diseases in the ‹64 age groups, the 2002 rate for Croatia was 24.5/100,000 and was below the standardized rate for Central and East Europe countries (30.0/100,000) and 2001 European average rate (30.0/100,000).

Cardiovascular diseases also are the leading cause of hospitalization with more than 76,871 hospitalizations in total and accounted for 13.8% of overall hospitalizations in Croatia in 2002, even before neoplasms with 13.1%. In 2002, the hospitalization rate was 1736.8/100,000. Cerebrovascular diseases were the third most common cause of hospitalization among cardiovascular diseases, accounting for 22.9%, immediately following ischemic heart dis-

larnih bolesti u svim dobnim skupinama više u muškaraca nego u žena.

Analiza smrtnosti prema spolu pokazuje da su za cerebrovaskularne bolesti opće stope smrtnosti 2003. godine, kao i ranijih godina, više u žena (211.7/100.000) nego u muškaraca (163,33/100.000), dok ukupna stopa iznosi 188,4/100.000. Razlog tome je veći broj umrlih žena u starijim dobnim skupinama, kao i znatno veći broj starijeg ženskog nego muškog stanovništva, što rezultira višom ukupnom stopom smrtnosti od cerebrovaskularnih bolesti u žena.

Najučestaliji uzrok smrti kao pojedinačna dijagnoza iz skupne cerebrovaskularnih bolesti u Hrvatskoj je moždani udar nespecificiran kao krvarenje ili infarkt (I64 X. rev. MKB SZO). Udio ove dijagnoze u broju umrlih od cerebrovaskularnih bolesti 2003. godine iznosio je 72,9%. Slijede posljedice cerebrovaskularnih bolesti (I69) s udjelom od 9,5% i intracerebralno krvarenje (I61) s udjelom od 8,1%.

Dobno standardizirane stope smrtnosti iz baze podataka SZO za program "Zdravlje za sve" za Hrvatasku iznosile su 2002. godine (zadnji usporedivi raspoloživi podaci) 482,5/100.000 za bolesti srca i krvnih žila ukupno, za ishemijsku bolest srca 159,5/100.000 te za cerebrovaskularne bolesti 145,3/100.000. Navedene stope bile su niže od prosjeka stopa zemalja Srednje i Istočne Europe za bolesti srca i krvnih žila ukupno (526,2/100.000) i ishemijske bolesti srca (184,1/100.000), a neznatno više za cerebrovaskularne bolesti (144,7/100.000). Navedne stope, međutim, više su od prosječnih stopa za Europu ukupno 2001. godine (zadnji usporedivi raspoloživi podaci) za kardiovaskularne bolesti (469,0/100.000) i cerebrovaskularne bolesti (137,5/100.000), a niže za ishemijske bolesti srca (219,9/100.000).

Međutim, za umrle od cerebrovaskularnih bolesti u dobi do 64 godine za Hrvatsku stopa je 2002. godine iznosila 24,5/100.000 i bila je niža od standardizirane stope za zemlje Srednje i Istočne Europe (30,0/100.000), kao i od prosjeka za Europu 2001. godine (30.0/100.000).

Kardiovaskularne bolesti su i vodeći uzrok hospitalizacija s ukupno preko 76.871 hospitalizacija i udjelom od 13.8% u ukupnom broju hospitalizacija u Hrvatskoj 2002. godine, a ispred novotvorina udio kojih iznosi 13,1%. Stopa hospitalizacije iznosila je 2002. godine 1736,8/100.000. Cerebrovaskularne bolesti nalazile su se na trećem mjestu uzroka hospitalizacije među kardiovaskularnim bolestima s udjelom od 22,9%, iza ishemijskih bolesti srca (26,5%) i ostalih oblika srčanih bolesti (šifre I30-I32 MKB SZO) (25,0%). Stopa hospitalizacije za cerebrovaskularne bolesti iznosila je 2002. godine 396,7/100.000.

eases (26.5%) and other cardiac diseases (WHO ICD I30-I32) (25.0%). In 2002, the rate of hospitalization for cerebrovascular diseases was 396.7/100,000.

In 2002, the most common cause of hospitalization from the group of cerebrovascular diseases was cerebral infarction (WHO ICD X rev., I63) with 41.0%, followed by stroke unspecified as hemorrhage or infarction (I64) with 29.4%, and intracerebral hemorrhage (I61) with 8.3%.

According to the number of diagnoses recorded in general medicine service in Croatia in 2002, cardiovascular diseases ranked second with 12.0%, immediately following respiratory diseases accounting for 25.0%. The rate of cardiovascular diseases registered at general medicine service was 184.9/1000. The most common diagnostic subgroup were hypertensive diseases with 54.2%, whereas cerebrovascular diseases ranked fifth with 5.8% and rate of 10.8/1000 diagnoses recorded at general medicine offices.

Najčešći uzrok hospitalizacije iz skupine cerebrovaskularnih bolesti 2002. godine bili su moždani infarkt (I63 X. rev. MKB SZO) s udjelom od 41,0%, inzult nespecificiran kao krvarenje ili infarkt (I64) s udjelom od 29,4% i intracerebralno krvarenje (I61) s udjelom od 8,3%.

Po broju dijagnoza zabilježenih u općoj medicini u Hrvatskoj 2002. godine kardiovaskularne bolesti nalaze se na drugom mjestu s udjelom od 12,0 %, iza bolesti dišnog sustava udio kojih je iznosio 25,0%. Stopa kardiovaskularnih bolesti registriranih u djelatnosti opće medicine iznosila je 184,9/1.000. Najučestalija dijagnostička podskupina bile su hipertenzivne bolesti s udjelom od 54,2%, dok su se cerebrovaskularne bolesti nalazile na petom mjestu s udjelom od 5,8% i stopom od 10,8/1.000 bolesti zabilježenih u općoj medicini.

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CLINICAL RELEVANCE OF STROKE EPIDEMIOLOGY STUDIES
KLINIČKO ZNAČENJE PROUČAVANJA EPIDEMIOLOGIJE MOŽDANOG UDARA

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Epidemiology as a science investigating the distribution of diseases and disability in human population as well as factors influencing this distribution (World Health Organization /WHO/, 1967) has specific tasks and goals. The most important tasks refer to investigation of the epidemiological importance of a disease and factors influencing individual and population health, identification of the causes and factors that contribute to the occurrence, spread and mode of disease dissemination, conducting epidemiological studies of a disease, and proposal and implementation of measures for prevention, control, elimination and eradication of diseases. In this way, the preset goals of epidemiology can be achieved, i.e.: reduction of morbidity, mortality and lethality of a particular disease, prevention of disability and disablement, and reduction of overall social and economic burden of the disease.

Like epidemiological investigations in general, the neuroepidemiological monitoring of stroke implies the use of descriptive, analytical and experimental studies. The use of epidemiological principles and methods in clinical medicine practice is known as clinical epidemiology. It is also defined as bedside epidemiology or "science of medical skill". Its goal is to reach a clear and rational decision on when and how to treat, what drug to choose, etc. It is a basic science allowing for evidence based medicine to be applied in clinical practice. The population based neuroepidemiological studies of stroke are important to determine stroke morbidity (incidence and prevalence) and mortality as well as longterm outcome of the disease. Clinical epidemiological studies enable early lethality and short-term outcome of stroke to be estimate.

The internationally accepted standards need to be employed in the epidemiological studies of stroke. WHO defines stroke as "abrupt development of clinical signs of focal (or global) impairment of cerebral functions with symptoms lasting for 24 hours or more, or leading to death, without any other apparent cause besides the signs of vascular lesion". In clinical practice, a classification has been widely accepted which takes in consideration the pathologic-anatomic and pathophysiologic parameters, and

Epidemiologija kao znanost koja proučava distribuciju bolesti i invalidnosti u ljudskoj populaciji i čimbenike koji utječu na takvu distribuciju (Svjetska zdravstvena organizacija /SZO/, 1967.) ima svoje specifične zadatke i ciljeve. Najvažniji zadaci odnose se na proučavanje epidemiološkog značenja bolesti i čimbenika koji utječu na zdravlje pojedinca i populacije, identifikaciju uzroka i čimbenika koji pridonose pojavi bolesti, rasprostranjenosti i načina širenja bolesti, provođenje epidemioloških istraživanja bolesti, te predlaganje i provođenje mjera sprječavanja, suzbijanja, uklanjanja i iskorjenjivanja bolesti. Na taj način moguće je ostvarivanje ciljeva epidemiologije, a to su: snižavanje pobola, smrtnosti i letaliteta određene bolesti, sprječavanje invalidnosti i nesposobnosti te smanjenje ukupnog socijalnog i ekonomskog tereta bolesti za društvenu zajednicu.

U neuroepidemiološkom praćenju moždanog udara (MU), kao i u epidemiološkim istraživanjima općenito rabe se deskriptivne, analitičke i eksperimentalne studije. Primjena epidemioloških načela i metoda u praksi kliničke medicine naziva se klinička epidemiologija. Definira se još i kao epidemiologija uz bolesnički krevet ili kao "znanost o umijeću medicine". Ona ima za cilj doći do jasne i racionalne odluke o tome kada liječiti, kako liječiti, koji lijek odabrati itd. To je bazična znanost koja omogućuje da se na dokazima utemeljena medicina primijeni u kliničkoj praksi. Populacijske neuroepidemiologijske studije MU važne su za utvrđivanje pobola (incidencije i prevalencije) i smrtnosti, te dugoročnog ishoda ove bolesti. Kliničke epidemiološke studije omogućuju procjenu ranog letaliteta i kratkoročnog ishoda MU.

U epidemiološkim istraživanjima MU u današnje je vrijeme nužno rabiti međunarodno prihvaćene standarde. SZO definira MU kao "naglo razvijanje kliničkih znakova žarišnog (ili globalnog) poremećaja moždanih funkcija sa simptomima koji traju 24 sata ili duže ili vode k smrti, bez drugog jasnog uzroka uza znakove oštećenja krvnih žila". U kliničkom radu široko je prihvaćena klasifikacija koja uzima u obzir patološko-anatomske i patofiziološke parametre, te razlikuje hemoragijski moždani udar (HMU)

differentiates between hemorrhagic stroke accounting for 15%-20% and ischemic stroke accounting for 80%-85% of cases. Hemorrhagic stroke subtypes are intracerebral hemorrhage of typical or atypical localization, which accounts for some 15%, and subarachnoid hemorrhage (SAH), which accounts for 5% of stroke cases. Subtypes of ischemic stroke include thrombotic, embolic and hemodynamic stroke. The International Classification of Diseases classifies cerebrovascular diseases (CVD) in almost the same way, listing the following subgroups encoded I60-I69: SAH, intracerebral hemorrhage, other nontraumatic hemorrhages, cerebral infarction caused by extracerebral or intracerebral occlusion, and nonspecific stroke. The TOAST classification of ischemic stroke has proved quite convenient and has recently been widely used, distinguishing the following categories: large blood vessel infarction, lacunar infarction, cardioembolic infarction, infarction due to other causes, and infarction of unknown causes.

Concepts on the presence of risk factors in stroke patients have resulted in numerous epidemiological studies of these factors conducted in the last few decades in Croatia and worldwide. The impact of some of these factors has been definitely demonstrated, whereas the role of others is still being investigated. Risk factors for stroke are generally classified according to the possibility of their prevention into nonmodifiable risk factors, including age, sex, heredity, race and/or ethnicity, and modifiable risk factors that include arterial hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, asymptomatic carotid stenosis, smoking and excessive alcohol consumption. Also, lifestyle related factors have been continuously investigated; these include inadequate physical activity, obesity, dietary habits, stress, socioeconomic factors, and illicit drug abuse. The role of hematology parameters (hematocrit, homocysteine, lipoprotein(a), fibrinogen, etc.), cardiac diseases (mitral valve prolapse, patent foramen ovale, atrial septal aneurysm) and other risk factors has also been investigated. The latest studies conducted in Croatia show a high level of risk factors in the healthy population, good population information on their harmful health impact, and quite a low level of motivation to modify unhealthy habits and lifestyle.

The basic neuroepidemiological parameters are important for every clinician dealing with a particular disease or group of diseases. Stroke incidence is the number of patients newly affected with stroke in a defined population over a particular period of time. The criteria for a properly designed study of the incidence of stroke imply the use of the standard WHO definition of stroke; prospective re-

koji se javlja u 15%-20% i ishemijski moždani udar (IMU) koji čini 80%-85% slučajeva. Podtipovi HMU su intracerebralno krvarenje tipične ili atipične lokalizacije, koje predstavlja oko 15%, te subarahnoidno krvarenje (SAH*)* koje predstavlja oko 5% slučajeva MU. Podtipovi IMU su trombotični, embolijski i hemodinamski udar. Međunarodna klasifikacija bolesti razvrstava CVB na približno isti način, navodeći pod šiframa I60-I69 slijedeće podskupine: SAH, intracerebralno krvarenje, ostala netraumatska krvarenja, cerebralni infarkt uzrokovan ekstracerebralnom ili intracerebralnom okluzijom, te nespecificirani moždani udar. Praktična je i u zadnje vrijeme u široj uporabi klasifikacija IMU nazvana TOAST koja razlikuje slijedeće kategorije: infarkte velikih krvnih žila, lakunarne infarkte, kadioembolijske infarkte, infarkte koji su posljedica drugih uzroka, te infarkte nepoznatog uzroka.

Spoznaje o prisutnosti rizičnih čimbenika u bolesnika s MU rezultirala su brojnim epidemiološkim istraživanjima o ovim čimbenicima koja su provedena tijekom zadnjih nekoliko desetljeća u svijetu i u Hrvatskoj. Utjecaj nekih čimbenika nedvojbeno je dokazan, a značenje drugih još uvijek se istražuje. Rizični čimbenici obično se svrstavaju prema mogućnostima njihovog sprječavanja u slijedeće skupine: nepromjenjivi čimbenici rizika (*nonmodifiable stroke risk factors*), među koje se ubrajaju dob, spol, nasljedni čimbenici, rasa i/ili etnička pripadnost i promjenjivi čimbenici rizika (*modifiable stroke risk factors*) kao što su arterijska hipertenzija, atrijska fibrilacija, šećerna bolest, hiperlipidemija, asimptomatska karotidna stenoza, pušenje, zlouporaba alkohola. Pod stalnim epidemiološkim istraživanjima su i rizični čimbenici povezani s načinom života (*lifestyle factors*), među koje spadaju tjelesna aktivnost, pretilost, prehrana, stres, socioekonomski čimbenici, zlouporaba opojnih droga. Istražuje se i uloga hematoloških parametara (hematokrit, homocistein, lipoprotein(a), fibrinogen itd.), srčanih bolesti (prolaps mitralne valvule, otvoren foramen ovale, atrijska septalna aneurizma) i drugih rizičnih čimbenika. Najnovija istraživanja provedena u našoj zemlji pokazuju visoku zastupljenost rizičnih čimbenika u zdravoj populaciji, dobru obaviještenost pučanstva o njihovoj štetnosti za zdravlje, ali i nisku razinu motivacije za promjenu navika i načina življenja.

Osnovni neuroepidemiološki pokazatelji važni su za svakog kliničara koji se bavi problematikom određene bolesti ili skupine bolesti. Incidencija je broj novooboljelih bolesnika od MU u definiranoj populaciji tijekom određenog vremenskog razdoblja. Kriteriji dobro dizajnirane studije incidencije MU uključuju upotrebu standardne definicije MU koju je dala SZO, prospektivno utvrđivanje

cording of cases in a large, well defined and representative sample; and comprehensive and distinct methodology of detecting the diseased and identifying nonfatal cases that have been treated outpatiently or died soon after the disease onset. The incidence of stroke in strict terms would refer to the cases of first-ever stroke, however, some studies also include recurrent stroke.

It is estimated that some 4 million people are affected with stroke in the world *per* year. International epidemiological studies show the stroke rates to grow exponentially with age, ranging between 0.3/1000 in the third and fourth decades of life to up to 30/1000 in the eighth and ninth decades of life, yielding a mean of 1/1000 to 2/1000. In Croatia, the last population based studies were performed some 20 years ago. Studies carried out on hospital material in the Osijek region over the past 15 years have indicated the number of stroke cases and of cerebral hemorrhages to be on constant increase (Fig. 1). Dietary and other daily habits and climatic factors have been identified as the main culprits for such a trend. However, the impact of socioeconomic factors (decline in living standards, social and economic problems, demographic changes, etc.) as well as of war and postwar stress on the incidence of stroke has also been investigated. These studies have pointed to the effect of prolonged stress on an increased expression of risk factors for CVD (arterial hypertension, hyperlipidemia, adiposity and smoking); adverse effects of stress and risk factors on cerebral hemodynamics; and association of stress with an increased incidence of cerebral hemorrhages, especially hypertensive intracerebral hemorrhage and SAH. Such trends have also been recorded in other war areas.

slučajeva u velikom, dobro definiranom i reprezentativnom uzorku te sveobuhvatnu i razumljivu metodologiju otkrivanja oboljelih i identifikacije nefatalnih slučajeva liječenih izvan bolnice ili umrlih ubrzo nakon nastupa bolesti. Incidencija MU, strogo gledajući, odnosila bi se na incidente koji se javljaju prvi put u životu neke osobe (*first-ever stroke*), ali neke studije obuhvaćaju i opetovane MU.

Procjenjuje se da u svijetu na godinu od MU oboli oko 4 milijuna ljudi. Međunarodne epidemiološke studije pokazuju kako stope rastu eksponencijalno s dobi i kreću se između 0,3 promila u trećem i četvrtom desetljeću života sve do 30 promila u osmom i devetom desetljeću života, što u prosjeku iznosi 1-2 promila. U našoj zemlji posljednje populacijske studije provedene su prije dvadesetak godina. Istraživanja provedena na osječkom području tijekom zadnjih petnaestak godina na bolničkom materijalu pokazuju stalan porast broja oboljelih od MU i stalan porast broja moždanih krvarenja (slika 1.). Način prehrane, životne navike i klimatski čimbenici navedeni su kao glavni uzročnici ovakvog stanja. Međutim, istraženo je i djelovanje socioekonomskih čimbenika (pad životnog standarda, socijalni i ekonomski problemi, demografske promjene itd.), te ratnog i poratnog stresa na incidenciju MU. Istraživanjima je utvrđen utjecaj produljenog stresa na povećanu izraženost čimbenika rizika za cerebrovaskularnu bolest (arterijske hipertenzije, hiperlipidemije, adipoziteta i pušenja), nepovoljan utjecaj stresa i rizičnih čimbenika na cerebralnu hemodinamiku, kao i povezanost stresa s povećanom incidencijom cerebralnih hemoragija, osobito hipertenzivnih intracerebralnih krvarenja i subarahnoidnih krvarenja. Ovakvi trendovi zabilježeni su i u drugim ratom zahvaćenim područjima.

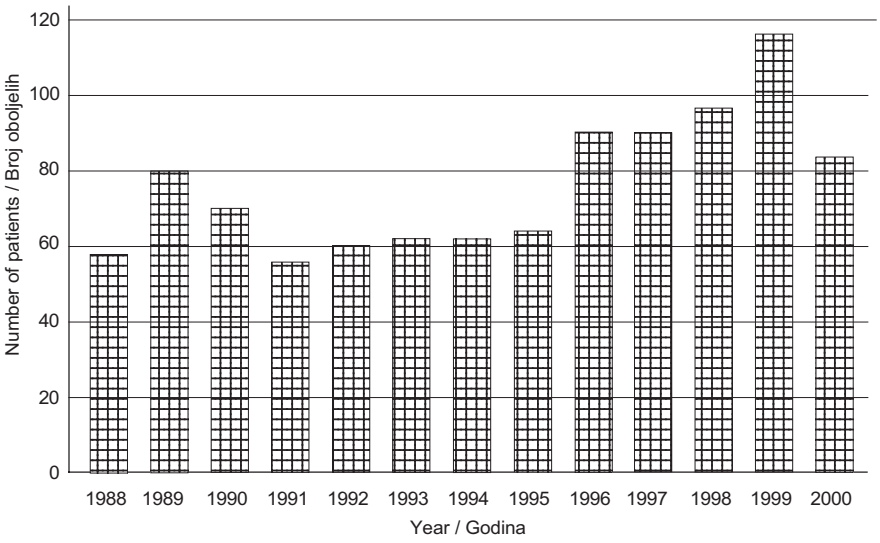

Figure 1. Number of hemorrhagic strokes treated at Department of Neurology Osijek in the threeteen years' period (1988-2000).

Slika 1. Kretanje broja hemoragičkih moždanih udara liječenih na Neurološkoj klinici u Osijeku u trinaestgodišnjem razdoblju

Prevalence is a parameter describing the magnitude of a disease and represents the frequency of the disease at a particular point of time. Data on stroke prevalence are the best indicator of the spread of the disease in a particular population, allowing for setting an appropriate strategy of health actions and overall health care in the area. The stroke prevalence rates vary from 5/1000 to several percent. The last data on stroke prevalence in Croatia were published in 1984. A study performed in a small sample of 1000 subjects indicated a stroke prevalence of 2.5%, and of 3.1% in the population over 25 years of age.

Lethality is the proportion of stroke patients that died within a specified period from the disease onset. It is usually expressed as the percentage of deaths over a period of one month or one year. The predictors influencing early lethality are localization and size of infarction or hemorrhage, degree of consciousness impairment, severity of neurologic deficit, advancing age, male sex, presence of diabetes, arterial hypertension, cardiac disease, elevated temperature, dysphagia, sphincter incontinence, etc. Fatal stroke outcome may be caused by central or peripheral complications. The most common central complications include cerebral edema, transtentorial herniation, hemorrhagic transformation of ischemia, epileptic seizures, and depression. In stroke patients death is considerably more frequently caused by peripheral (systemic) complications such as deep venous thrombosis and pulmonary embolism, bronchopneumonia, urinary infection, septicemia, aspiration, cardiac arrhythmia, myocytolysis, nonregulated hypotension, and sudden death.

Mortality is the number of deaths due to stroke in a defined population. Stroke mortality rates, mostly expressed as the number of deaths *per* 100,000 population *per* year, greatly vary across Europe. The highest stroke mortality rate has been reported from Bulgaria (249/100,000), and lowest from Switzerland (27/100,000). East European countries have a higher total mortality, whereas lowest mortality rates have been recorded in Scandinavian countries, Switzerland and the Netherlands. Stroke mortality rates have been dramatically reduced over the last few decades in Japan and West European countries. In contrast to this, a constantly growing trend has been observed in this period for stroke mortality rates in East European countries, which is evidently being continued in the conditions of transition in these countries. Studies revealing secular changes in the particular disease mortality over a longterm period of years or decades are of special interest. On analyzing the secular death pattern, data on the age, period and cohort (generation) effects have to

Prevalencija je pokazatelj koji opisuje veličinu problema neke bolesti i predstavlja učestalost te bolesti u određenom trenutku. Podaci o prevalenciji moždanog udara najbolji su pokazatelj proširenosti bolesti u populaciji i omogućuju postavljanje ispravne strategije zdravstvenih akcija i cjelokupne zdravstvene zaštite na određenom području. Stope prevalencije MU u svijetu kreću se između 5 promila i nekoliko postotaka. Zadnji podaci o prevalenciji MU u Hrvatskoj objavljeni su 1984. godine. Istraživanjem provedenim u malom uzorku od 1000 stanovnika utvrđena je prevalencija MU od 2,5% odnosno 3,1% za populaciju iznad 25 godina starosti.

Letalitet je udio bolesnika oboljelih od MU koji su umrli unutar specifičnog razdoblja nakon nastupa bolesti. Izražava se obično kao postotak umrlih u razdobljima od jednog mjeseca i jedne godine. Predskazatelji koji utječu na ranu smrtnost su: lokalizacija i veličina infarkta ili krvarenja, stupanj poremećaja svijesti, težina neurološkog deficita, rastuća dob, muški spol, prisutnost šećerne bolesti, arterijske hipertenzije, srčane bolesti, povišene temperature, disfagije, inkontinencije sfinktera itd. Fatalan ishod MU uzrokuju središnje i periferne komplikacije. Najčešće središnje komplikacije su: cerebralni edem, transtentorijalna hernijacija, hemoragijska transformacija ishemije, epileptični napadaji, depresija. Znatno češće smrt bolesnika s MU uzrokuju periferne (sistemske) komplikacije: duboka venska tromboza i plućna embolija, bronhopneumonija, mokraćni infekt, septikemija, aspiracija, srčana aritmija, miocitoliza, nekontrolirana hipotenzija, nagla smrt.

Smrtnost je broj umrlih od MU u definiranoj populaciji. Stope smrtnosti koje se najčešće izražavaju kao broj umrlih od MU na 100.000 stanovnika u jednoj godini u Europi značajno variraju. Najviše stope od 249 zabilježene u Bugarskoj, a najmanje od 27 u Švicarskoj. Istočnoeuropske zemlje imaju višu ukupnu smrtnost, dok su najniže stope zabilježene u skandinavskim zemljama, Švicarskoj i Nizozemskoj. Stope smrtnosti dramatično su smanjene tijekom zadnjih nekoliko desetljeća u Japanu i zapadnoeuropskim zemljama. Nasuprot tome, u istočnoeuropskim zemljama u tom razdoblju bilježi se stalan porast stope srmtnosti od MU, što se nastavlja i u uvjetima tranzicije ovih zemalja. Od osobitog su značenja studije koje pokazuju sekularne promjene u smrtnosti od neke bolesti kroz dugo razdoblje od više godina ili desetljeća. Za analizu sekularnog trenda umiranja treba uzeti u obzir dobne, periodske i kohortne (generacijske) učinke. Analiza sekularnog kretanja umiranja od CVB u Hrvatskoj u razdoblju od 1957. do 1997. (Kadojić D. i Babuš V.) pokazala je da se nastavlja sekularni

Table 1. Number of deaths and proportional mortality rates for CVD in the population aged 35-74 in Croatia, by 5-years periods

Tablica 1. Broj umrlih i proporcionalne stope smrtnosti od CVB u populaciji u dobi od 35-74 godina u Hrvatskoj prema petgodišnjim razdobljima

Petgodišnje razdoblje	Number of death / Broj umrlih		Prportional mortality rates % Proporcionalna stopa smrtnosti %	Chain indeks Lančani indeks*
	All causes Svi uzroci	CVD CVB		
1958.-1962.	18.913	2.831	9,0	–
1963.-1967.	20.806	2.072	10,0	111
1968.-1972.	25.751	2.918	11,3	113
1973.-1977.	24.658	3.318	13,5	119
1978.-1982.	25.975	3.656	14,1	104
1983.-1987.	25.611	3.822	14,9	106
1988.-1992.	25.311	3.588	14,2	95
1993.-1997.	26.788	3.959	14,8	104

* index according to previous period

* indeks prema prethodnom razdoblju

be taken in consideration. Analysis of the secular death pattern due to CVD in Croatia during the 1957-1997 period (Kadojić D and Babuš V) has shown the secular rising trend of the number of deaths (Table 1) and of the proportional rate of CVD mortality (Table 2) in the 35-74 age groups to continue. The mortality rates are especially high in the inland area, in the towns of Osijek and Varaždin, occasionally being 2- to 3-fold those recorded in the coastal area. Comparison of our data with those from other countries has shown the overall age-adjusted mortality rates in Croatia to exceed European average rate as well as the average rates in Central and East Europe for all age groups, whereas the rates for the 0-64 age group were lower than the latter.

The disease risk shows the likelihood for an individual to be affected by a particular disease during life. This analysis implies the use of at least two criteria for the confidence of association between a particular risk factor exposure and the risk of disease. Relative risk is the relationship between the disease incidence among those with and without exposure to a particular risk factor. Attributive risk is absolute incidence of a disease in exposed individuals that can be ascribed to the risk exposure. This measure is calculated by subtracting the disease incidence in unexposed individuals from total disease incidence. It is usually presented as the number of individuals from a population who will be affected with a particular disease and is expressed as the rate *per* 1000 population.

Clinical studies of short-term and longterm stroke outcomes and of the economic burden of the disease also are of great interest. It has been estimated that approximately one third of stroke patients still die, one third suf-

trend rasta ukupnog broja umrlih (tablica 1.) i rast proporcionalne stope smrtnosti od CVB (slika 2.) u populaciji od 35 od 74 godina starosti. Stope umiranja su osobito visoke na kontinentalnom području, u gradovima Osijeku i Varaždinu, te ponegdje dostižu 2-3 puta više vrijednosti negoli u priobalnom području. Usporedba naših podataka s podacima iz drugih zemalja pokazuje da su u nas dobno standardizirane stope smrtnosti za sve dobi ukupno više od europskog prosjeka i prosjeka zemalja Srednje i Istočne Europe, dok su ove stope za dobnu skupinu od 0 do 64. godine niže od prosjeka Srednje i Istočne Europe.

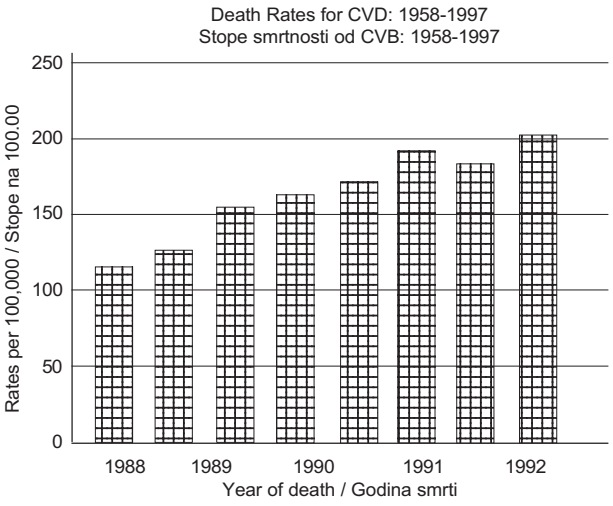

Figure 2. Standardized mortality rates for CVD in Croatia in the population aged 35-74 in Croatia, by 5-years periods

Slika 2.Standardizirane stope mortaliteta od CVB u populaciji 35-74 godina starosti u Republici Hrvatskoj, prema petogodišnjim razdobljima

fer severe neurologic deficit, and one third sustain milder or no neurologic deficit. The factors predicting poor stroke prognosis and outcome are advanced age, male sex, coexistence of diabetes mellitus, arterial hypertension, cardiac disease, elevated temperature, dysphagia, incontinence, consciousness disturbances, severe neurologic deficit, cognitive impairment, localization and size of infarction, edema and central structure dislocation, biochemistry and hematology disorders, etc. Our studies of short-term and longterm ischemic stroke outcome have shown that approximately one fourth of patients die within one month, and a half within six months. The 5-year mortality for ischemic stroke is even up to 60%. First-ever strokes account for some 75%, and recurrent strokes for 25% of cases. The risk of stroke recurrence is highest during the first year after stroke, being around 10%, then 5% for each year. The most important predictors of recurrent stroke are type of stroke, previous TIA, arterial hypertension, cardiac valve disease, atrial fibrillation, congestive heart failure, elevated blood glucose, male sex, and alcohol abuse.

Conclusion

Epidemiological data show stroke to be the leading medical and public health problem in Croatia. While large population based epidemiological studies are lacking, the analyses performed on hospital material over the last 15 years provide an insight into the current state and point to unfavorable trends in stroke morbidity and mortality in our country. The present system of care for stroke patients does not meet the needs and is not in accordance with the modern trends in Europe and elsewhere in the world. Thus, there is a real need of the system restructuring. One of the options might be the development and implementation of the National Project of Stroke Prevention and Treatment, on the model of other transition countries in Europe that have faced similar problems and epidemiological parameters. The following strategic points should be set for the Project: 1) analysis of stroke epidemiology in Croatia, with due reference to regional variation (population-based studies, hospital-based studies, hospital stroke registers, etc.); b) reducing the incidence of stroke through improved primary and secondary prevention; and c) reducing stroke lethality, disability and mortality through establishment of stroke units and improving the system of patient rehabilitation. In the interim, the current principles of diagnosis, management and prevention of stroke, accepted in the USA and West European countries, should be followed, and favorable experience of the leading Croatian neurologists engaged in the field should be used. In

Rizik obolijevanja je broj koji govori koliki su izgledi da određena osoba tijekom svoga života oboli od neke bolesti. U analizi postoje barem dva mjerila za pouzdanost povezanosti između izloženosti određenom rizičnom čimbeniku i rizika obolijevanja. Relativan rizik je odnos incidencije bolesti onih koji su izloženi i incidencije onih koji nisu izloženi nekom čimbeniku rizika. Atributivni rizik je apsolutna incidencija bolesti kod izloženih pojedinaca koja se može pripisati toj izloženosti. Ova se mjera dobije tako da se incidencija određene bolesti kod neizloženih osoba oduzme od ukupne incidencije. Obično se izražava brojem osoba koje će u populaciji oboljeti od neke bolesti i izražava se stopom na 1000 stanovnika.

Od velikog su značenja i kliničke studije kratkoročnog i dugoročnog ishoda MU i ekonomskog tereta bolesti. Procjenjuje se kako još uvijek otprilike jedna trećina oboljelih od moždanog udara umire, druga trećina ima teži, a treća trećina lakši ostatni neurološki deficit ili je bez deficita. Čimbenici koji predviđaju lošu prognozu i ishod MU su: visoka životna dob, muški spol, postojanje šećerne bolesti, arterijske hipertenzije i srčane bolesti u oboljelih, temperatura, disfagija, inkontinencija, pogoršanje svijesti, težak neurološki deficit, kognitini poremećaji, lokalizacija i veličina infarkta, edem i pomak središnjih struktura, biokemijski i hematološki poremećaji itd. Naša istraživanja kratkoročnog i dugoročnog ishoda ishemijskog MU pokazuju kako u prosjeku oko četvrtine bolesnika umire u prvom mjesecu, a oko polovice unutar šest mjeseci. Smrtnost u petgodišnjem razdoblju nakon ishemijskog MU kreće se i do 60%. Među oboljelima otprilike 75% slučajeva čine prvi, a 25% slučajeva recidivirajući MU. Rizik recidiva moždanog udara najveći je u prvoj godini i kreće se oko 10%, a svake slijedeće godine oko 5%. Najvažniji predskazatelji recidiva MU su: vrst udara, raniji prolazni ishemijski napadaji (TIA), arterijska hipertenzija, bolest srčanog zaliska, atrijska fibrilacija, kongestivna srčana slabost, visoka razina glukoze u krvi, muški spol i zlouporaba alkohola.

Zaključak

Epidemiološki podaci pokazuju da u našoj zemlji MU predstavlja vodeći medicinski i javnozdravstveni problem. Iako nedostaju opsežnije populacijske epidemiološke studije, analize provedene na bolničkom materijalu u zadnjih petnaestak godina ipak daju određenu sliku stvarnog stanja i ukazuju na nepovoljne trendove u obolijevanju i umiranju od ove bolesti. Postojeći sustav zbrinjavanja bolesnika s MU ne zadovoljava potrebe i nije u skladu sa suvremenim trendovima u Europi i svijetu. Postoji realna potreba reorganizacije toga sustava. Jedna od mogućih

addition, the Guidelines for Stroke Prevention and Treatment, issued by the Croatian Society for Neurovascular Disorders, are of great help to the clinicians.

opcija je priprema i provođenje Nacionalnog projekta prevencije i liječenja moždanog udara, po uzoru na druge tranzicijske zemlje u Europi koje imaju slične probleme i epidemiološke pokazatelje. Strateške točke toga projekta trebaju biti: a) analiza epidemiologije MU u Hrvatskoj s osvrtom na regionalne razlike (populacijske studije, bolničke studije, bolnički registri MU), b) snižavanje incidencije MU kroz bolju primarnu i sekundarnu prevenciju, c) snižavanje letaliteta, invaliditeta i smrtnosti od ove bolesti organizacijom jedinica za liječenje MU i unapređenjem sustava rehabilitacije bolesnika. U međuvremenu treba slijediti suvremena načela u dijagnostici, liječenju i sprječavanju MU, koja su prihvaćena u zapadnoeuropskim zemljama i SAD, te rabiti pozitivna iskustva vodećih domaćih neuroloških stručnjaka koji se bave ovom problematikom. Uz to, za liječnike kliničare od velikog su značenja i pomoći "Smjernice za liječenje i prevenciju moždanog udara" koje izdaje Hrvatsko društvo za neurovaskularne poremećaje.

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NEUROTRANSMITTERS AND STROKE
NEUROTRANSMITERI I MOŽDANI UDAR

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PREVENTION OF STROKE
PREVENCIJA MOŽDANOG UDARA

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Introduction

Although therapeutic procedures to reduce cerebral damage cuased by ischemic stroke (thrombolysis) have recently been developed, prevention remains the most efficient strategy to decrease the prevalence of stroke.

In the last few decades, a significant decrease in the stroke mortality has been recorded in most western countries. In the USA, the mortality of stroke was reduced by 60% from the beginning of the 1970s to the end of 1990s. This trend is believed to have been almost exclusively achieved through modification of the risk factors for stroke. It has been demonstrated that stroke can be prevented and the risk of stroke recurrence reduced.

Uvod

Mada su zadnjih godina razvijeni terapijski postupci kojima se može smanjiti oštećenje mozga nastalo ishemijskim moždanim udarom (tromboliza), prevencija je i nadalje najučinkovitija strategija za smanjivanje učestalosti moždanog udara. U većini zapadnih zemalja zabilježen je značajan pad smrtnosti od moždanog udara u zadnjim desetljećima. U Sjedinjenim Američkim Državama smrtnost od moždanog udara smanjena je za 60% od početka sedamdesetih do kraja devedesetih godina prošloga stoljeća. Smatra se da je taj trend postignut gotovo isključivo modificiranjem čimbenika rizika za nastanak moždanog udara. Pokazalo se da se moždani udar može spriječiti, kao i da se može smanjiti rizik recidiva moždanog udara.

Prevention implies the procedures taken in patients to prevent the onset of stroke. Prevention has traditionally been divided into primary and secondary prevention. Primary prevention refers to the measures taken in healthy subjects who have not yet been affected with stroke. Secondary prevention refers to identification and management of subjects at a very high risk of stroke in order to prevent its onset, and treatment and rehabilitation of patients who have sustained a stroke to prevent its recurrence.

Primary and secondary prevention of stroke improve the patient quality of life, reduce the need of surgical procedures, prolong overall survival, and decrease the incidence of stroke recurrence. There is major overlapping between the procedures and strategies of primary and secondary prevention of stroke.

The following measures are used in primary prevention of stroke:

1) lifestyle related risk factors should be addressed in order to modify an unhealthy lifestyle and to promote a health one;
2) diseases that represent risk factors for stroke should be treated, thus reducing the effect of these risk factors increasing the prevalence of stroke;
3) in case of ischemic stroke, certain drugs such as peroral anticoagulants and antiaggregation therapy are prescribed in addition to addressing the risk factors involved; and
4) in case of significant carotid artery stenosis, operative therapy for carotid stenosis is performed.

There is ample evidence that various circumstances, conditions, behavior, daily habits and diseases are associated with the incidence of stroke, and are thus called risk factors for the occurrence of stroke.

Risk Factors for Stroke

- Nonmodifiable risk factors:
  - age
  - sex
  - race
  - heredity
  - family history of stroke
  - personal history of stroke and/or transient ischemic attack (TIA)
- Modifiable risk factors:
  - lifestyle related factors:
    smoking
    alcoholism
    drug abuse
    physical inactivity and obesity

Prevencija označava postupke koji se poduzimaju kod bolesnika kako bi se spriječio nastanak moždanog udara. Tradicionalno se prevencija dijeli na primarnu i sekundarnu. Primarna prevencija obuhvaća prevenciju u zdravih osoba koje još nisu oboljele, odnosno koje još nisu zadobile moždni udar. Sekundarna prevencija predstavlja identificira-nje i liječenje osoba s vrlo visokim rizikom za nastanak moždanog udara kako bi se spriječio njegov nastanak, te liječenje i rehabilitaciju bolesnika koji su preboljeli moždani udar kako bi se spriječio nastanak novog moždanog udara.

Primarnom i sekundarnom prevencijom moždanog udara može se poboljšati kvaliteta života, smanjiti potreba za kirurškim zahvatima, produžiti ukupno preživljavanje te smanjiti učestalost budućih moždanih udara. Postupci i strategije primarne i sekundarne prevencije moždanog udara uvelike se preklapaju.

U okviru prevencije moždanog udara primjenjuju se slijedeći postupci:

1. potrebno je djelovati na čimbenike rizika povezane s načinom života u cilju otklanjanja nezdravog načina života i promicanja zdravog načina života
2. liječiti bolesti koje predstavljaju rizične čimbenike i na taj način smanjivati utjecaj tih rizičnih čimbenika na povećanje učestalosti moždanog udara
3. u slučaju ishemijskog moždanog udara uz djelovanje na čimbenike rizika propisuju se i određeni lijekovi: peroralni antikoagulansi i antiagregacijska terapija
4. u slučaju značajne stenoze karotidnih arterija pristupa se operacijskom liječenju karotidne stenoze

Postoji mnoštvo dokaza da su razne okolnosti, stanja, ponašanje, životne navike i bolesti značajno povezani s incidencijom moždanog udara, pa se stoga nazivaju čimbenicima rizika za nastanak moždanog udara.

Čimbenici rizika za nastanak moždanog udara

- Čimbenici na koje se ne može utjecati:
  - dob
  - spol
  - rasa
  - nasljeđe
  - moždani udar u obiteljskoj amanezi
  - podatak o prethodnom moždanom udaru i/ili prethodnim prolaznim ishemijskim napadajima (TIA)
- Čimbenici na koje se može utjecati:
  - povezani s načinom života:
    pušenje
    alkoholizam
    zlouporaba droga
    tjelesna neaktivnost i pretilost

unhealthy dietary habits
stress
oral contraceptives

– diseases and states:
hypertension
cardiac diseases: atrial fibrillation and other cardiac arrhythmias
valvular diseases
cardiomyopathy
extensive myocardial infarction
endocarditis
cardiac aneurysm
open foramen ovale
left ventricular hypertrophy
transient ischemic attacks (TIA)
significant carotid artery stenosis (>75% of lumen)
elevated cholesterol
diabetes mellitus
hyperhomocysteinemia
hypercoagulability
elevated hematocrit and blood hyperviscosity
vasculitides

nezdrava prehrana
stres
upotreba oralnih kontraceptiva

– bolesti i bolesna stanja:
hipertenzija
srčane bolesti: atrijska fibrilacija i ostale srčane aritmije
bolesti srčanih zalistaka
kardiomiopatija
opsežni infarkt miokarda
endokarditis
aneurizma srca
otvoren foramen ovale
hipertrofija lijeve klijetke
prolazni ishemijski napadaji (TIA)
značajna stenoza karotidnih arterija (stenoza >75% lumena)
povišen kolesterol
šećerna bolest
hiperhomocistinemija
hiperkoagulabilnost
povišen hematokrit i stanja hiperviskoznosti krvi
vaskulitisi

Nonmodifiable risk factors for stroke

Age is one of the most significant risk factors for stroke. The risk of stroke is known to rise by approximately 10% with each decade of life after the age of sixty.

Considering sex, men are known to be more prone to stroke in the reproductive age than women. However, after the menopause the risk of stroke rises in female population. This and the fact that life expectancy is longer in women result in female predominance in the absolute number of stroke cases in the advanced age groups.

A family history of stroke and/or personal history of stroke or TIA significantly increase the likelihood of stroke in such a patient. The incidence of stroke is higher in subjects with prior TIA or stroke.

Nonmodifiable risk factors for stroke

Lifestyle related risk factors

Cigarette smoking contributes significantly to the prevalence of stroke. A meta-analysis of 32 studies has shown that smoking increases the risk of stroke by 50%. A dose-dependent relationship was also demonstrated, i.e. the risk of stroke increased with the number of cigarettes. Quitting smoking was associated with a rapid decrease in the risk of stroke; Framingham study revealed the risk of stroke

Čimbenici rizika za nastanak moždanog udara na koje se ne može utjecati

Dob. Dob je jedan od najznačajnijih čimbenika rizika za nastanak moždanog udara. Poznato je da nakon šezdesete godine života rizik za nastanak moždanog udara raste za otprilike 10% sa svakim slijedećim desetljećem starosti.

Spol. Poznato je da su muškarci skloniji nastanku moždanog udara u generativnoj životnoj dobi. Međutim, nakon menopauze rizik od nastanka moždanog udara raste u ženskoj populaciji. Ta činjenica i podatak da je prosječni životni vijek u žena duži dovodi do pojave da u starijoj životnoj dobi u apsolutnom broju ima više žena s moždanim udarom.

Podatak o moždanom udaru u obiteljskoj anamnezi i/ili podatak o preboljelom moždanom udaru ili TIA u osobnoj anamnezi značajno podižu mogućnost nastanka moždanog udara u dotičnog bolesnika. Osobe s preboljelim TIA ili moždanim udarom češće će zadobivaju ponovni moždani udar.

after 5 years of stopping smoking to be the same as in nonsmokers.

Physical inactivity and overweight

Framingham study pointed to a negative correlation between physical activity and stroke prevalence in male population. Recent studies indicate that an increased level of physical activity is associated with a decrease in the risk of stroke also in women, and that abdominal obesity is a significant independent risk factor for stroke. The favorable effect of increased physical activity on lowering the risk of stroke is considered to be due to its action in decreasing elevated blood pressure and body weight as well as to improved glucose tolerance. Also, a higher level of physical activity increases HDL cholesterol, lowers LDL cholesterol, and promotes a healthy lifestyle.

Alcohol abuse certainly is a significant risk factor for stroke. Our studies have shown that blood vessels of an alcoholic are on an average 10 years older than the subject's biological age. However, the intake of small amounts of alcohol (up to two drinks daily) has been associated with reduction of the risk of ischemic stroke. According to some data, one glass of red wine daily is optimal, as red wine contains flavonoids that act as antioxidants. The risk of ischemic stroke rises abruptly with the intake of more than two alcoholic drinks daily. A J-shaped association has been determined between the intake of alcoholic drinks and incidence of stroke: the incidence of ischemic stroke decreases with the intake of up to two drinks daily, whereas an increased intake of alcohol is associated with a higher incidence of both ischemic and hemorrhagic stroke.

Stress reaction enhances platelet aggregation and activates renin-angiotensin system, thus increasing the production of angiotensin II which leads to blood pressure elevation. In this way, stress increases the prevalence of cardiovascular and cerebrovascular diseases. However, there are difficulties in exact stress defining as well as in the methodology of measuring stress "intensity". Only a limited number of studies investigating the impact of stress on the prevalence of stress are available in the literature, most of them describing the relationship between war related stress and prevalence of stroke. Data from these studies are suggestive of an association between stress and an increased prevalence of hemorrhagic stroke.

As for drug abuse, the use of cocaine, especially in its alkaloid form ("crack") has been association with an increased prevalence of cerebrovascular disease, both ischemic and hemorrhagic.

Considering oral contraceptives, the risk of stroke is increased in women taking these agents, especially those

Čimbenici rizika za nastanak moždanog udara na koje se može utjecati

Čimbenici povezani s načinom života

Pušenje. Pušenje cigareta značajno doprinosi učestalosti moždanog udara. Metaanaliza 32 studije pokazala je kako pušenje povisuje rizik od nastanka moždanog udara za 50%. Također je pokazana ovisnost o dozi: rizik od nastanka moždanog udara povećava se s brojem popušenih cigareta. Prestanak pušenja povezan je s brzim smanjivanjem rizika nastanka moždanog udara; Framinghamska studija pokazala je da se nakon pet godina nepušenja rizik od nastanka moždanog udara izjednačava s rizikom u nepušača.

Tjelesna neaktivnost i prekomjerna tjelesna težina. U Framinghamskoj studiji pokazana je negativna povezanost tjelesne aktivnosti i učestalosti moždanog udara u muškoj populaciji. Novija istraživanja pokazuju da je povećana tjelesna aktivnost povezana sa smanjivanjem rizika moždanog udara i u žena, te da je abdominalni tip pretilosti značajan neovisan čimbenik rizika za nastanak moždanog udara. Smatra se da je povoljan učinak povećane tjelesne aktivnosti na snižavanje rizika za nastanak moždanog udara posljedica učinka na snižavanje povišenih vrijednosti tlaka, smanjivanje tjelesne težine i poboljšanje tolerancije glukoze. Povećana tjelesna aktivnost također dovodi do povišenja HDL kolesterola i snižavanja LDL kolesterola, te do promicanja zdravog načina života.

Alkohol. Zlouporaba alkohola svakako predstavlja značajan čimbenik rizika za nastanak moždanog udara. Naša istraživanja pokazala su da su krvne žile alkoholičara prosječno deset godina starije od biološke starosti alkoholičara. Međutim, pijenje malih količina alkohola (do dva pića na dan) povezano je sa snižavanjem rizika za nastanak ishemijskog moždanog udara. Postoje podaci koji govore kako je najbolje uzimanje jedne čaše crnog vina na dan, jer se u crnom vinu nalaze flavonoidi koji djeluju kao antioksidansi. Rizik od nastanka ishemijskog moždanog udara značajno raste ako se popiju više od dva alkoholna pića na dan. Utvrđena je povezanost pijenja alkoholnih pića i učestalosti moždanog udara u obliku slova J: incidencija ishemijskog moždanog udara se smanjuje pri pijenju do dva alkoholna pića na dan, a kod povećanog unosa alkohola raste učestalost ishemijskog i hemoragijskog moždanog udara.

Stres. Reakcija na stres povećava agregaciju trombocita, aktivira sustav renina-angiotenzina i na taj način povećava stvaranje angiotenzina II. koji povisuje krvni tlak. Stoga stres uzrokuje povećanu učestalost kardiovaskularnih i cerebrovaskularnih bolesti. Međutim, postoje teškoće u točnom definiranju stresa i načinu mjerenja "jačine" stre-

containing high estrogen. Whether oral contraceptives with a low dose of estrogen increase the risk of stroke yet remains a matter of dispute. The use of oral contraceptives has been demonstrated to increase the risk of stroke in those women who also have other stroke risk factors (age >35, hypertension, smoking). A World Health Organization study conducted in developing countries showed the risk of cerebral hemorrhage to be significantly higher in women taking oral contraceptives. Oral contraceptives have also been associated with an increased risk of subarachnoidal hemorrhage, which is especially pronounced in women with coexistent hypertension.

Treatment of Diseases Representing Risk Factors for Stroke

Hypertension

Hypertension is the most significant risk factor for stroke. The prevalence of stroke increases with diastolic and systolic pressure elevation. The prevalence of stroke rises by 46% with every 7.5 mm Hg increase in diastolic pressure. The Systolic Hypertension in the Elderly Program (SHEP) has shown the treatment of isolated systolic hypertension in subjects older than 60 leads to a 36% decrease in the prevalence of stroke.

The risk of stroke is considerably reduced by the treatment of hypertension. A meta-analysis of 14 randomized clinical trials has shown a diastolic arterial pressure reduction of 5-6 mm Hg to significantly decrease the prevalence of stroke by 42%. It should be noted that hypertension has to be treated and arterial pressure values maintained within the normal limits, i.e. at least below 140/90 mm Hg rather than just reduce the level of arterial pressure. May some other risk factor be also present (e.g., diabetes mellitus), the blood pressure level should be maintained below 130/80 mm Hg. It has recently been shown that in addition to their favorable effect on blood pressure lowering, the use of newer antihypertensives (angiotensin converting enzyme /ACE/ inhibitors, new generations of lipophilic calcium channel blockers, and angiotensin receptor blockers) also has an additional beneficial action in the prevention of vascular diseases. This has been attributed to their possible effect on vascular walls, especially on endothelial cells. Such an action of new antihypertensives may also be observed in patients with normal blood pressure.

Atrial fibrillation

Atrial fibrillation is one of the most significant independent risk factors for stroke. Atrial fibrillation has been assosa. Objavljeno je svega nekoliko radova o utjecaju stresa na učestalost moždanog udara, a većina članaka opisuje utjecaj stresa povezanog s ratnim zbivanjima i učestalosti moždanog udara. Podaci iz navedenih studija upućuju ne moguću povezanost stresa i povećane učestalosti hemoragijskog moždanog udara.

Zlouporaba opojnih droga. Upotreba kokaina, pogotovo u njegovom alkaloidnom obliku (*crack*), povezana je s povećanom učestalošću cerebrovaskularne bolesti, kako ishemijske tako i hemoragijske.

Oralni kontraceptivi. Rizik od nastanka moždanog udara povećan je u žena koje uzimaju oralne kontraceptive, pogotovo oralne kontraceptive s visokim sadržajem estrogena. Još uvijek nije jasno povećavaju li oralni kontraceptivi s malom dozom estrogena rizik od nastanka moždanog udara. Dokazano je kako uzimanje oralnih kontraceptiva povećava rizik nastanka moždanog udara u žena koje imaju i druge čimbenike rizika (žene starije od 35 godina, hipertenzija, pušenje). U studiji Svjetske zdravstvene organizacije u zemljama u razvoju rizik od moždanog krvarenja bio je značajno veći kod žena koje su uzimale oralne kontraceptive. Oralni kontraceptivi su povezani i s povećanjem rizika subarahnoidnog krvarenja, što je naročito izraženo u žena koje imaju i hipertenziju.

Liječenje bolesti koje predstavljaju čimbenike rizika za nastanak moždanog udara

Hipertenzija

Hipertenzija je najznačajniji čimbenik rizika za nastanak moždanog udara. Učestalost moždanog udara povećava se kod povišenog dijastoličnog i sistoličnog tlaka. Učestalost moždanog udara raste 46% za svakih 7,5 mm Hg porasta dijastoličnog tlaka. U studiji Systolic Hypertension in the Elderly Program (SHEP) pokazalo se je kako liječenje izolirane sistolične hipertenzije u osoba starijih od 60 godina dovodi do smanjenja učestalosti moždanog udara za 36%.

Liječenje hipertenzije značajno smanjuje rizik od moždanog udara. Metaanaliza 14 randomiziranih kliničkih pokusa pokazala je kako smanjenje dijastoličnog arterijskog tlaka od 5-6 mm Hg uzrokuje značajno smanjenje učestalosti moždanog udara od 42%. Značajno je napomenuti da treba liječiti hipertenziju i održavati vrijednosti arterijskog tlaka u normalnim granicama, tj. barem ispod 140/90 mm Hg, a ne samo sniziti arterijski tlak. Ako je prisutan i neki drugi čimbenik rizika (npr. šećerna bolest), tada treba tlak održavati ispod 130/80 mm Hg.

U zadnje vrijeme pokazalo se je kako primjena novijih antihipertenziva (inhibitori enzima konverzije angioten-

ciated with approximately 5-fold increase in the incidence of first ever stroke. Controlled clinical trials have shown that the risk of stroke in patients with atrial fibrillation can be reduced by 70% with the use of oral anticoagulant (warfarin).

In patients below the age of 65 with atrial fibrillation, therapy with oral anticoagulants should be introduced and INR (international normalized ratio) values maintained at 2.5 (range 2.0-3.0), which appears to be adequate for successful prevention of stroke while not being associated with an increased risk of hemorrhage. Patients aged >65 with isolated atrial fibrillation and those who cannot take oral anticoagulants for any reason can take acetylsalicylic acid (ASA) at a dose of 100-300 mg/day. Anticoagulant therapy should not be prescribed in patients with a history of hemorrhagic stroke.

Elevated cholesterol

Data from recent studies indicate that there is an association between elevated levels of cholesterol and incidence of stroke. Subsequent analysis of for pravastatin studies (where stroke was not set as a primary endpoint) revealed a significant reduction in the incidence of stroke in patients taking pravastatin. Subsequent analysis of data obtained in the Scandinavian Simvastatin Survival Study (4S) showed a 28% relative stroke and TIA risk reduction. The Cholesterol And Recurrent Events (CARE) study showed a 31% relative stroke risk reduction, whereas in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study the relative risk reduction for stroke was 19%. Subsequent analysis of 16 published studies on the impact of statins on the incidence of stroke and general mortality revealed that the relative risk of stroke was decreased by 19% with the use of statins, thus pointing to the beneficial effect of cholesterol lowering on the incidence of stroke. Besides cholesterol lowering, statins may also have some additional favorable effects, i.e. soft plaque stabilization, improved endothelial function, and reduced platelet aggregation. Statins may also lead to a decrease in the intimal-medial thickness, thus offering the possibility of their use in patients with atherosclerotic plaques but normal cholesterol levels.

Diabetes mellitus

Diabetes mellitus is an independent risk factor for the development of atherosclerosis and stroke. A twofold mortality rate following ischemic stroke has been found in diabetic patients relative to nondiabetic subjects. However, a strict control of blood glucose has not been definitely

zina /inhibitori ACE/, novije generacije lipofilnih blokatora kalcijevih kanala, te blokatori angiotenzinskih receptora) uz povoljno djelovanje na snižavanje krvnog tlaka ima i dodatan povoljni učinak u prevenciji krvožilnih bolesti, koji se pokušava objasniti učinkom na stijenku krvnih žila, a prvenstveno na endotelne stanice. Takvo djelovanje novijih antihipertenziva možda je moguće i u bolesnika s normalnim krvnim tlakom.

Atrijska fibrilacija

Atrijska fibrilacija je jedan od najznačajnijih neovisnih čimbenika rizika za nastanak moždanog udara. Atrijska fibrilacija povisuje učestalost moždanog udara otprilike pet puta za prvi moždani udar. Kontrolirane kliničke studije su pokazale kako se primjenom peroralnih antikoagulansa (varfarin) može smanjiti rizik od nastanka moždanog udara u bolesnika s atrijskom fibrilacijom za otprilike 70%.

U bolesnika mlađih od 65 godina s atrijskom fibrilacijom u okviru prevencije moždanog udara potrebno je uvesti terapiju peroralnim antikoagulansima i održavati vrijednosti INR (*international normalized ratio*) na 2,5 (raspon između 2,0 i 3,0), što je dovoljno za uspješnu prevenciju nastanka moždanog udara, a nije povezano s povećanim rizikom krvarenja. Bolesnici stariji od 65 godina koji imaju izoliranu atrijsku fibrilaciju i oni bolesnici koji iz bilo kojeg razloga ne mogu uzimati peroralne antikoagulanse, mogu uzimati acetilsalicilnu kiselinu u dozi između 100 i 300 mg na dan. Antikoagulantna terapija ne smije se propisivati bolesnicima koji su preboljeli hemoragijski moždani udar.

Povišen kolesterol

Podaci iz novijih studija pokazuju da postoji povezanost između povišenih vrijednosti kolesterola i učestalosti moždanog udara. Naknadna analiza četiri studije s pravastatinom (u kojima moždani udar nije bio unaprijed postavljen kao primarni krajnji ishod) pokazala je značajno smanjenje učestalosti moždanog udara u bolesnika koji su uzimali pravastatin. U Skandinavskoj studiji preživljavanja sa simvastatinom (Scandinavian Simvastatin Survival Study – 4S) naknadna analiza podataka otkrila je relativno smanjenje rizika za moždani udar i TIA za 28%. U studiji Cholesterol And Recurrent Events (CARE) pokazano je relativno smanjenje rizika od moždanog udara za 31%, a u studiji Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) relativno smanjenje rizika za moždani udar iznosilo je 19%. Naknadna analiza 16 objavljenih studija o utjecaju statina na učestalost moždanog udara i opću smrtnost pokazala je kako primjenom statina dolazi do smanjivanja relativnog rizika moždanog udara za 29%, što

confirmed to act favorably on the prevention of stroke. In type 2 diabetic patients, therapy with oral hypoglycemic agents and/or insulin has been demonstrated to improve systemic microvascular complications but not macrovascular complications such as stroke. A more precise determination of the independent impact of diabetes mellitus on the occurrence and development of stroke is believed to be hampered by the presence of many other risk factors for stroke that are already present at the time of diabetes diagnosis.

Significant carotid artery stenosis

A stenosis of ³75% of the lumen is considered as significant carotid arterial stenosis (according to the criteria set by the European Carotid Surgery Trial, ECST), or of ³50% of the lumen (according to the criteria set by the North American Symptomatic Carotid Endarterectomy Trial, NASCET). In Croatia, the ECST criteria are generally used. Significant carotid arterial stenosis is associated with a high risk of ipsilateral stroke.

All patients diagnosed with significant carotid artery stenosis should be referred to a vascular surgeon for endarterectomy, which should be performed at an institution with perioperative and postoperative mortality and morbidity below 3%. In case of asymptomatic carotid stenosis, the ACAS study demonstrated favorable impact in men with 60%-99% stenosis but in female population. Most experts now believe that patients with significant carotid artery stenosis should be operated on at an institution with a perioperative risk below 3%, however, some think that in case of asymptomatic carotid stenosis the decision should be made on an individual basis.

Medication in Secondary Prevention of Ischemic Stroke

Antiaggregation therapy

Antiaggregation agents are prescribed for secondary prevention of ischemic stroke. The most commonly prescribed agents are ASA, ticlopidine, clopidogrel and dipyridamole. A collaborative group of antiaggregation therapy investigators has published an overview of controlled clinical trials of the use of antiaggregation agents in the prevention of vascular diseases. The analysis included 145 studies with more than 51,000 patients, and concluded that the use of antiaggregation therapy led to a 22% relative risk reduction for all vascular diseases and 23% relative risk reduction for stroke.

ukazuje na povoljan učinak snižavanja vrijednosti kolesterola na učestalost moždanog udara. Uza snižavanje kolesterola, izgleda da bi statini mogli imati i dodatne povoljne učinke: stabiliziranje mekanih plakova, poboljšanje funkcije endotela, smanjenje agregacije trombocita. Statini bi mogli smanjivati debljinu intime i medije (*intimal-medial thickness*), čime se otvara mogućnost primjene statina u bolesnika s aterosklerotskim plakovima, a s normalnim vrijednostima kolesterola.

Šećerna bolest

Šećerna bolest predstavlja neovisan čimbenik rizika za nastanak ateroskleroze i moždanog udara. U osoba sa šećernom bolešću utvrđena je dvostruko viša smrtnost nakon ishemijskog moždanog udara u odnosu na osobe bez šećerne bolesti. Međutim, nije dokazano da stroga kontrola koncentracije glukoze u krvi djeluje povoljno na sprječavanje moždanog udara. U bolesnika s dijabetesom tip II. pokazalo se je kako terapija peroralnim hipoglikemicima i/ili inzulinom poboljšava sistemske mikrovaskularne komplikacije, ali ne i makrovaskularne komplikacije kao što je moždani udar. Smatra se da je preciznije određivanje neovisnog udjela šećerne bolesti u nastanku i razvoju moždanog udara otežano zato što postoji niz drugih čimbenika rizika za nastanak moždanog udara koji su već prisutni pri otkrivanju šećerne bolesti.

Značajna stenoza karotidnih arterija

Značajnom stenozom karotidnih arterija smatra se stenoza jednaka ili veća od 75% lumena (prema kriterijima European Carotid Surgery Trial - ECST), odnosno jednaka ili veća od 50% (prema kriterijima North American Symptomatic Carotid Endarterectomy Trial - NASCET). U Hrvatskoj se uglavnom primjenjuju kriteriji ECST-a. Značajna stenoza karotidne arterije povezana je s izraženim rizikom od nastanka istostranog moždanog udara.

Sve bolesnike u kojih se dijagnosticira značajna stenoza karotidne arterije treba uputiti vaskularnom kirurgu da se učini endarterektomija u centru koji ima perioperacijsku i poslijeoperacijsku smrtnost i pobol niže od 3%.

Za asimptomatsku karotidnu stenozu je studija ACAS pokazala povoljan učinak u muškaraca sa stenozom od 60%-99%, ali ne i u ženskoj populaciji. Većina stručnjaka danas smatra kako bolesnike sa značajnom stenozom karotidne arterije treba operirati u centru koji ima rizik operacije manji od 3%, mada u slučaju asimptomatske karotidne stenoze neki smatraju da odluku treba donijeti individualno.

Acetylsalicylic acid

Acetylsalicylic acid (ASA) is a medication discovered more than a hundred years ago. ASA inhibits cyclo-oxygenase, thus preventing the synthesis of thromboxane A2 (TXA2) in platelets, and the synthesis of prostacycline (PGI2) in endothelial cells. The collaborative group of investigators for antiplatelet agents found a 25% relative stroke risk reduction in patients taking ASA. The optimal dose of ASA in the prevention of stroke has not yet been definitely determined. ASA doses from 30 to 1500 mg/day have been used in various trials. Studies failed to show any major differences among low (<100 mg/day), medium (100-500 mg/day) and high (>500 mg/day) ASA doses. Low doses have been postulated to be more efficacious than medium and high doses, because the former act on TXA2 synthesis in platelets but not to the same extent on PGI2 synthesis in endothelial cells. It seems that ASA in any dose greater than 30 mg/day reduces the risk of stroke, whereby higher doses are associated with an increased incidence of ASA side effects (gastrointestinal bleeding, gastrointestinal discomfort, heartburn, nausea, vomiting). Therefore, lower ASA doses (100-300 mg/day) should be prescribed for ischemic stroke prevention.

Ticlopidine

Ticlopidine is a tienopyridine derivative blocking the adenosine-diphosphate pathway of platelet aggregation. In the Canadian-American Ticlopidine Study (CATS), ticlopidine in a dose of 500 mg/day led to a 33% stroke risk reduction. In the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine in a dose of 500 mg/day reduced the risk of stroke or death by 12% in comparison with ASA in a dose of 1300 mg/day. Ticlopidine is as efficacious or even more efficacious than ASA in secondary stroke prevention. However, the drug is associated with a major disadvantage of common side effects such as diarrhea, rash, as well as serious side effects such as neutropenia, thrombocytopenia, thrombocytopenic thrombocytic purpura and pancytopenia. Ticlopidine is a drug with more serious side effects than ASA. Most side effects related to bone marrow functioning occur within three months of ticlopidine introduction in therapy, therefore patients should undergo frequent blood count controls during this period. However, thrombocytopenic thrombocytic purpura may also develop after this initial period.

Clopidogrel (not registered in Croatia)

Clopidogrel is chemically similar to ticlopidine, also blocking the adenosine-phosphate pathway of platelet

Lijekovi u sekundarnoj prevenciji ishemijskog moždanog udara

Antiagregacijska terapija

U sekundarnoj prevenciji ishemijskog moždanog udara propisuju se antiagregacijski lijekovi. Najpropisivaniji su lijekovi acetilsalicilna kiselina (ASK), tiklopidin, klopidogrel i dipiridamol.

Suradna grupa ispitivača za antiagregacijske lijekove objavila je pregled kontroliranih kliničkih studija primjene antiagregacijskih lijekova u prevenciji krvožilnih bolesti. Analizirane su 145 studije u kojima je bilo uključeno više od 51.000 bolesnika. Zaključeno je kako primjena antiagregacijskih lijekova dovodi do relativnog smanjenja rizika od svih vaskularnih bolesti za 22%. U slučaju moždanog udara relativno smanjenje rizika iznosilo je 23%.

Acetilsalicilna kiselina

Acetilsalicina kiselina (ASK) je lijek otkriven pred više od stotinu godina. ASK inhibira ciklooksigenazu i na taj način sprječava sintezu tromboksana A2 (TXA2) u trombocitima, ali i sintezu prostaciklina (PGI2) u endotelnim stanicama. U publikaciji Suradna grupa ispitivača za antitrombocitne lijekove utvrdila je relativno smanjenje rizika moždnog udara za 25% u bolesnika koji su uzimali ASK. Optimalna doza ASK u prevenciji moždanog udara još uvijek nije nedvojbeno utvrđena. U raznim istraživanjima primjenjivale su se doze ASK od 30 do 1500 mg/dan. Istraživanja nisu pokazala značajnih razlika između malih (<100 mg/dan), srednjih (100-500 mg/dan) i visokih doza (>500 mg/dan). Pretpostavlja se da su male doze učinkovitije od srednjih i visokih, jer djeluju na sintezu tromboksana A2 u trombocitima, a ne djeluju u tolikoj mjeri na sintezu prostaciklina u stanicama endotela. Izgleda da ASK u svakoj dozi većoj od 30 mg/dan smanjuje rizik moždanog udara, a veće doze povezane su s višom učestalošću nuspojava ASK (krvarenje iz probavnog trakta, probavne smetnje, žgaravica, mučnina, povraćanje). Stoga bi u prevenciji ishemijskog moždnog udara trebalo propisivati niže doze ASK od 100-300 mg/dan.

Tiklopidin

Tiklopidin je tienopiridinski derivat koji blokira adenozin-difosfatni put agregacije trombocita. U istraživanju Canadian-American Ticlopidine Study (CATS) tiklopidin u dozi od 500 mg/dan doveo je do 33%-tnog smanjenja rizika nastanka moždanog udara. U istraživanju Ticlopidine Aspirin Stroke Study (TASS) tiklopidin u dozi od 500 mg/dan smanjio je rizik nastanka moždanog udara ili smrti za

aggregation. In the Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, clopidogrel at a dose of 75 mg/day in comparison with ASA at a dose of 325 mg/day led to an 8.7% relative risk reduction for vascular disease. As differentiated from ticlopidine, clopidogrel does not induce substantially more side effects than ASA. Clopidgrel is slightly more efficient than the medium doses of ASA. Clopidogrel is the drug of choice for secondary stroke prevention in patients who cannot tolerate ASA. Considering their different mechanisms of action, a combination of ASA and clopidogrel proved quite interesting. However, results of the recently published MATCH study indicate that the addition of ASA to clopidogrel did not lead to any significant difference in the vascular event reduction, whereas a higher incidence of bleeding was recorded in the group of patients coadministered ASA and clopidogrel.

Dipyridamole (not registered in Croatia)

Dipyridamole is considered to prevent platelet aggregation in a number of ways, i.e. by inhibiting phosphodiesterase, thus increasing the level of antithrombotic cyclic adenosine monophosphate in platelets; by inhibiting cellular uptake and metabolism of adenosine, thus increasing the plasma concentration of adenosine; and by directly stimulating the release of prostacycline from endothelial cells. In the European Stroke Prevention Study 1 (ESPS-1), a combination of ASA in a dose of 990 mg/day and dipyridamole in a dose of 225 mg/day led to a 38% relative stroke risk reduction. The European Stroke Prevention Study 2 (ESPS-2) demonstrated a relative reduction of 18% for ASA at a dose of 50 mg/day, 16% for dipyridamole at a dose of 400 mg/day, and 37% for the combination of ASA and dipyridamole in the same doses. Previous small studies failed to show any significant difference between the use of ASA alone and in combination with dipyridamole. A combination of ASA at a dose of 25 mg and dipyridamole at a dose of 200 mg used twice daily could be the therapy of choice in the prevention of stroke.

Most authors believe that in the secondary prevention of stroke, antiaggregation agents should be used as long as there is the risk of stroke occurrence, which in the majority of patients means for life.

Oral anticoagulants for stroke prevention

Some 20% of strokes are of cardioembolic origin, most commonly due to with atrial fibrillation, acute myocardial infarction, left ventricular wall thrombosis, rheumatic heart disease, artificial valves. Therapy with oral anticoagulant

12% u usporedbi s ASK u dozi od 1300 mg/dan. Tiklopidin je ili podjednako učinkovit u sekundarnoj prevenciji moždanog udara kao i ASK ili čak i učinkovitiji od ASK. Medutim, glavni nedostatak ovoga lijeka su nuspojave kao dijareja, osipi, te ozbiljne nuspojave kao neutropenija, trombocitopenija, trombocitopenična trombotična purpura i pancitopenija. Tiklopidin je lijek s više ozbiljnih nuspojava od ASK. Većina nuspojava povezanih s funkcijom koštane srži nastaje u prva tri mjeseca nakon uvođenja tiklopidina u terapiju, pa u tom vremenu treba bolesnicima učestalo kontrolirati krvnu sliku. Međutim, trombocitopenična trombotična purpura može nastati i nakon tog vremena.

Klopidogrel (lijek nije registriran u Hrvatskoj)

Klopidogrel je lijek kemijski sličan tiklopidinu, koji također blokira adenozin-difosfatni put agregacije trombocita. U studiji Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) je klopidogrel u dozi od 75 mg/dan u usporedbi s ASK u dozi od 325 mg/dan doveo do relativnog smanjenja rizika vaskularnih bolesti za 8,7%. Za razliku od tiklopidina, klopidogrel nema bitno većih nuspojava od ASK. Klopidogrel je nešto učinkovitiji od srednjih doza ASK. Klopidogrel predstavlja lijek izbora u sekundarnoj prevenciji moždnog udara u bolesnika koji ne podnose ASK. S obzirom na različit mehanizam djelovanja zanimljiva je bila kombinacija ASK i klopidogrela. Međutim, rezultati nedavno objavljene studije MATCH pokazali su kako dodavanjem ASK klopidogrelu nije postignuta značajna razlika u smanjenju vaskularnih događaja, a u skupini bolesnika koja je primala ASK i klopidogrel zabilježena je veća učestalost krvarenja.

Dipiridamol (lijek nije registriran u Hrvatskoj)

Smatra se da dipiridamol sprječava agregaciju trombocita na više načina: inhibirajući fosfodiesterazu, što dovodi do povećanja razine antitrombotskog cikličnog adenozin monofosfata u trombocitima; inhibiranjem staničnog preuzimanja i metabolizma adenozina, a time povećanja koncentracije adenozina u plazmi; te izravnim poticanjem otpuštanja prostaciklina iz endotelnih stanica. U European Stroke Prevention Study (ESPS-1) je kombinacija ASK u dozi od 990 mg/dan i dipiridamola u dozi od 225 mg/dan dovela do relativnog smanjenja rizika moždanog udara za 38%. Ispitivanje European Stroke Prevention Study 2 (ESPS-2) pokazala je relativno smanjenje rizika od 18% za ASK u dozi od 50 mg/dan, 16% za dipiridamol u dozi od 400 mg/dan i 37% za kombinaciju ASK i dipiridamola u istim dozama. Prijašnja manja istraživanja nisu pokazala

agents for the prevention of cardioembolic stroke should be considered in all these conditions that are associated with the potential causes of embolism. Dicumarol oral anticoagulants are used in the prevention of stroke to achieve INR between 2.0 and 3.0. In patients with atrial fibrillation, the risk of stroke is thus reduced while not increasing significantly the risk of hemorrhage. Although data from large, controlled studies are lacking, oral anticoagulants have been routinely prescribed to patients with artificial cardiac valves, where INR should be maintained between 3.0 and 4.0. Longterm therapy with oral anticoagulants to maintain INR between 2.0 and 3.0 should also be considered in patients with rheumatic disease of cardiac valves, other cardiac arrhythmias (except for atrial fibrillation), myocardial infarction, cardiac failure, cardiomyopathy, and in those with open foramen ovale. Patients who cannot take oral anticoagulants for whatever reason, can use ASA in a dose of 100-300 mg/day.

Conclusion

Each and every physician can contribute to stroke prevention in his/her daily practice. A healthy lifestyle should be encouraged on a daily basis, i.e. nonsmoking, giving up smoking, graded physical activity (30-minute exercise daily), overweight reduction and maintenance of desirable body weight (body mass index /BMI/ 18.5-24.9 kg/m^2), and healthy dietary habits (large amounts of fruit and vegetables, and reduced intake of saturated fat, cholesterol, salt and meat – Mediterranean diet), advising one to two alcoholic drinks daily (especially red wine), and discouraging excessive alcohol intake.

In hypertensive subjects, hypertension should be treated and arterial blood pressure maintained within the normal limits, i.e. at least up to 140/90 mm Hg or 130/80 mm Hg in diabetic persons. Patients with elevated cholesterol levels should be advised to adopt appropriate dietary habits, along with introducing statin therapy and maintaining cholesterol below 5 mmol/L and LDL cholesterol below 3 mmol/L. In diabetic patients, blood glucose values should be maintained as close to normal as possible. Patients with atrial fibrillation should be prescribed anticoagulant (INR 2.5, range 2.5-30) or ASA (300 mg/day) therapy. Patients with significant carotid arterial stenosis (>75%) should be advised to undergo operative treatment.

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značajnu razliku između primjene ASK same ili u kombinaciji s dipiridamolom. U prevenciji moždanog udara kombinacija ASK u dozi od 25 mg i dipiridamola u dozi od 200 mg, koja se primjenjuje dva puta na dan, može biti lijek prvog izbora.

Većina autora drži da antiagregacijske lijekove u sekundarnoj prevenciji moždanog udara treba primjenjivati sve dok postoji rizik nastanka moždanog udara, što u većine bolesnika znači doživotno.

Terapija oralnim antikoagulansima u prevenciji moždanog udara

Oko 20% moždanih udara je kardioembolijskog podrijetla, a najčešći izvori su atrijska fibrilacija, akutni infarkt miokrada, tromboza stijenke lijeve klijetke, reumatska bolest srca, umjetni zalisci i slično. O terapiji oralnim antikoagulansima treba razmisliti u svim tim stanjima koja su povezana s mogućim uzrocima embolizma radi prevencije kardioembolijskih moždanih udara. U prevenciji moždanog udara primjenjuju se dikumarolski oralni antikoagulansi radi postizanja INR vrijednosti između 2,0 i 3,0 u bolesnika s atrijskom fibrilacijom, čime se smanjuje rizik od nastanka moždnog udara, a ne povećava se značajno rizik od krvarenja. Mada nedostaju podaci iz velikih kontroliranih istraživanja, oralni antikoagulansi se rutinski propisuju bolesnicima s umjetnim srčanm zaliscima, gdje vrijednost INR treba održavati između 3,0 i 4,0. O dugotrajnoj terapiji peroralnim antikoagulansima s održavanjem vrijednosti INR između 2,0 i 3,0 treba razmisliti i u bolesnika s reumatskim bolestima srčanih zalistaka, drugim srčanim aritmijama (osim atrijske fibrilacije), infarktom miokarda, popuštanjem srca, kardiomiopatijom i u bolesnika s otvorenim foramenom ovale. Bolesnici koji iz bilo kojeg razloga ne mogu uzimati peroralne antikoagulanse mogu uzimati ASK u dozi između 100 i 300 mg na dan.

Zaključak

Zapravo svaki liječnik u svojoj svakodnevnoj praksi može doprinijeti prevenciji moždanog udara. Svakodnevno treba poticati zdrav način života: nepušenje odnosno prestanak pušenja, doziranu tjelesnu aktivnost (30 minuta vježbanja svakoga dana), smanjivanje prekomjerne i održavanje poželjne tjelesne težine (indeks tjelesne mase /BMI/ 18,5-24,9 kg/m^2) i primjenu zdravih načina prehrane (veće količine voća i povrća u prehrani, smanjiti unos zasićenih masnoća, kolesterola, soli i crvenog mesa – mediteranska dijeta), savjetovati pijenje jednog do dva alkoholna pića na dan (a pogotovo crno vino), a sprječavati prekomjerno pijenje alkoholnih pića.

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U hipertoničara treba liječiti hipertenziju i održavati vrijednosti arterijskog tlaka u normalnim granicama, tj. barem ispod 140/90 mm Hg, odnosno ispod 130/80 mm Hg u dijabetičara. U bolesnika s povišenim vrijednostima kolesterola savjetovati dijetu i započeti terapiju statinima, održavati kolesterol ispod 5 mmol/L, a LDL kolesterol ispod 3 mmol/L. U dijabetičara održavati vrijednosti šećera što bliže normalnim, u bolesnika s atrijskom fibrilacijom ordinirati antikaogulanse (INR 2,5 /2,0-3,0/) ili ASK (300 mg/dan), u bolesnika sa značajnom stenozom karotidnih arterija (>75%) savjetovati operacijsko liječenje.

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RECOGNITION AND SIGNIFICANCE OF RISK FACTORS IN CROATIAN POPULATION
SPOZNAVANJE I ZNAČENJE RIZIČNIH ČIMBENIKA HRVATSKOG PUČANSTVA

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Summary

It is of utmost importance to identify the population risk factors for cerebrovascular diseases in order to determine the pathology and prevention as well as management of these diseases. Numerous studies have been published on the topic of risk factors in the population of Croatia, however, mostly for a particular region and in a small number of people. It was only in the 1995-1997 period that a comprehensive investigation of risk factors was conducted including 10,000 individuals of both sexes aged 18-65. Data on the prevalence of risk factors among the Croatian population were obtained by statistical analysis of data on 5,840 individuals from all parts of Croatia.

These data are quite disturbing, as they have revealed a high prevalence of bad habits with adverse health impact among the Croatian population (inappropriate dietary habits, inadequate physical activity, cigarette smoking) and an emerging necessity of undertaking an organized action within the health insurance system and health care system. Despite our knowledge, the epidemiologic indicators of cerebrovascular disease morbidity and mortality have not yet started to improve.

Introduction

The dynamics of new knowledge and scientific advances has enabled an unimaginable development of technologies that fundamentally change human life and living habits even within a single generation. The picture of diseases and disease states has also been altered accordingly, along with increase in life expectancy. In the second half of the 20th century, an association was recognized between certain living habits and occurrence of longterm, chronic noncontagious diseases. Then, systematic studies in the field were launched, the first and most famous of them being the Framingham Study, which confirmed the existence of risk factors that favor the onset of circulation disorders. Numerous other studies and projects followed to verify the great possibilities of preventive measures in the control of circulatory disorders, among which cerebrovascular diseases rank highest on the scale of death causes. In the 1980s and 1990s, similar investigations were conducted in Croatia, however, only in a limited number of individuals.

Sažetak

Spoznavanje rizičnih čimbenika je vrlo važno kako bi se procijenila patologija i prevencija te liječenje cerebrovaskularnih bolesti. Objavljeni su brojni radovi na temu rizičnih čimbenika u pučanstvu Republike Hrvatske, ali većinom za pojedinu regiju i mali broj ljudi. Sveobuhvatnije istraživanje rizičnih čimbenika na 10.000 osoba obaju spolova u dobi od 18 do 65 godina provedeno je tek u razdoblju između 1995. i 1997. godine. Podaci o učestalosti rizičnih čimbenika u hrvatskom pučanstvu dobili su se statističkom obradom podataka za 5.840 osoba iz svih dijelova Hrvatske. Ovi su podaci uznemirujući, jer otkrivaju visoku učestalost loših životnih navika među stanovništvom (loše prehrambene navike, nedovoljna tjelesna aktivnost, pušenje) i pozivaju na pokretanje organiziranog djelovanja unutar sustava zdravstvenog osiguranja i zdravstva općenito. Usprkos ovim spoznajama, epidemiološki pokazatelji pobola i smrtnosti od cerebrovaskularnih bolesti još se ne popravljaju.

Uvod

Dinamika novih spoznaja i znanstvenih otkrića omogućila je neslućeni razvoj tehnologija koje iz temelja mijenjaju život i životne navike čovjeka već u jednoj generaciji. Sukladno se mijenja slika bolesti i bolesnih stanja uz produženje životnog vijeka. U drugoj polovici 20. stoljeća uočena je povezanost određenih ljudskih navika s nastankom dugotrajnih kroničnih nezaraznih bolesti. Započeta su i sustavna istraživanja, od kojih je prvo i najpoznatije obuhvaćeno Framinghamskom studijom, koja su potvrdila postojanje rizičnih čimbenika koji pospješuju nastajanje cirkulacijskih bolesti. Slijedila su brojna druga istraživanja i projekti koji su potvrdili velike mogućnosti primjene prevencijskih mjera u suzbijanju cirkulacijskih bolesti, od kojih cerebrovaskularne bolesti zauzimaju na ljestvici uzroka smrti najviša mjesta.

Osamdesetih i devedesetih godina prošloga stoljeća provedena su slična istraživanja u Hrvatskoj, no uglavnom na manjem broju ispitanika.

Epidemiološki podaci

Cerebrovaskularne bolesti su jedan od vodećih uzroka smrti u nas, a noviji epidemiološki podaci ukazuju na sve veći pobol od bolesti cirkulacijskog sustava (tablica 1.).

Epidemiologic Data

Cerebrovascular diseases are one of the leading causes of death in Croatia, and recent epidemiologic data indicate an ever increasing tendency in the circulatory system morbidity (Table 1).

Table 1. Number of hospitalized patients according to years

Disease	Year				
	1976	1981	1992	2000	2002
Circulation	44,235	45,715	44,991	77,095	76,871
Nervous system	20,842	20,859	19,894	14,459	15,240

Source: Croatian Health Statistics Annals 1976,1981,1992, 2003.

The role of major risk factors reflects in the epidemiologic data presented. According to the HZZJZ report for 2002, the number of deaths according to the mortality rate (1980-2002) was quite constant, with some changes of up to 0.7%. There was an obvious increase in the number of deaths among those older than 65, which was due to the prolonged life expectancy (Table 2). According to the same source, in 1985 the life expectancy for women and men was 75.19 and 67.63 years, respectively, whereas in 2001 it was 78.17 for women and 71.03 for men.

Table 2. Number of deaths in the Republic of Croatia 1992-2002

Year	No. of deaths	%	Deaths in >65 age group
1992	51,800	11.6	33,727
1993	50,846	11.4	34,522
1994	49,482	11.1	33,928
1995	50,536	11.3	34,970
1996	50,636	11.3	35,841
1997	51,964	11.4	37,234
1998	52,311	11.6	38,394
1999	51,953	11.4	38,384
2000	50,246	11.5	37,749
2001	49,552	11.2	37,429
2002	50,569	11.4	38,832

Source: Croatian Health Statistics Annals 2002.

According to the Croatian Health Statistics Annals 2002, analysis of the leading causes of death in the Croatian population showed cerebrovascular disease to be on the high second place. In 2002, a total of 8,369 (16.55%) individuals of both sexes died from cerebrovascular diseases,

Tablica 1. Broj bolnički liječenih osoba po godinama

Bolesti	Godina				
	1976	1981	1992	2000	2002
Krvotoka	44,235	45,715	44,991	77,095	76,871
Živčanog sustava	20,842	20,859	19,894	14,459	15,240

Izvor: HZZJZ, Hrvatski zdravstveno statistički ljetopis 1976.,1981.,1992., 2003.

Značenje rizičnih čimbenika ogleda se u postojećim epidemiološkim podacima. Prema izvješću HZZJZ za 2002. godinu broj umrlih po godinama prema stopi umrlih (1980.-2002.) je gotovo stabilan uz promjene unutar 0,7% . Očit je porast broja umrlih starijih od 65 godina, što je odraz produženog životnog vijeka (tablica 2.). Prema istom izvoru očekivani prosječni životni vijek bio je 1985. za žene 75,19 godina, a za muškarce 67,63 godine, dok je 2001. godine bio za žene 78,17 godina, a za muškarce 71,03 godine.

Tablica 2. Broj umrlih u Republici Hrvatskoj od 1992. do 2002. god.

Godina	Broj umrlih	%	Umrli >65 godina
1992	51,800	11.6	33,727
1993	50,846	11.4	34,522
1994	49,482	11.1	33,928
1995	50,536	11.3	34,970
1996	50,636	11.3	35,841
1997	51,964	11.4	37,234
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1999	51,953	11.4	38,384
2000	50,246	11.5	37,749
2001	49,552	11.2	37,429
2002	50,569	11.4	38,832

Izvor: HZZJZ, Hrvatski zdravstveno statistički ljetopis 2002.

Analiza vodećih uzroka smrti hrvatskog pučanstva za 2002. godinu prema Hrvatskom zdravstveno statističkom ljetopisu na drugo mjesto stavlja cerebrovaskularnu bolest. Te je godine zbog cerebrovaskularnih bolesti umrlo ukupno 8.369 (16,55%) osoba obaju spolova, tj. 3.616 (14,05%) muškaraca i 4.753 (19,14%) žena. Za žene je 2002. godine poremećaj moždane cirkulacije bio na prvom mjestu vodećih uzroka smrti. Sveukupno je od bolesti cirkulacijskog sustava te godine umrlo 52,80% svih umrlih u Hrvatskoj.

i.e. 3,616 (14.05%) men and 4,753 (19.14%) women. In 2002, cerebrovascular disorder was the leading cause of death in female population. In 2002, 52.80% of all deaths were caused by circulation disorders.

During the year 2002, 76,871 (13.8%) patients were hospitalized for circulation disorders during 108,875 days. About 50% of those hospitalized at neurology departments were treated for cerebrovascular disease.

Risk Factors in the Crotian Population

During the 1995-1997 period, a study of risk factors in Croatia was carried out as part of the First Croatian Health Project. It was the first multicenter, randomized, comprehensive study including 10,000 subjects from urban and rural settings in the littoral and inland of Croatia. Field studies were performed at 30 locations in the Osijek, Zagreb, Rijeka and Split areas. The final sample included 5,840 subjects of both sexes aged 18-65. Analysis of the data collected by a questionnaire and blood sample testing showed the prevalence of risk factors in the Croatian population. Study results indicated a high prevalence of modifiable risk factors.

The prevalence of elevated blood pressure (BP ^{3}140/90 mm Hg) was found to be 45%, with a male predominance (52% *vs* 37.9%). Blood pressure values increased significantly with age.

Smoking was recorded in 32.6% of adults, also showing a male predominance (34.1% *vs* 26.6%).

Physical activity was present in only 4.3% of women and 17.1% of men, with 2-4 and 4-5 hours weekly, respectively.

Overweight (body mass index, BMI 25.0-29.9) was recorded in 41.4%, and obesity (BMI >30.0) in 18.0% of study subjects. The proportion of obese subjects increased with age in both sexes, showing highest rate in the Zagreb area. The rate of obesity was significantly higher in men (21%) than in women (15%).

The mean (c±SD) concentration of cholesterol (mmol/L) was higher in men than in women (5.81±1.36 *vs* 5.66±1.29). Ten percent of men and women had a mean cholesterol level exceeding 7.55 mmol/L and 7.39 mmol/L, respectively.

Triglyceride concentrations (mmol/L) were also greater in men (2.13±1.69) than in women (1.41±0.94). Some 10% of men and women had triglyceride levels exceeding 3.94 mmol/L and 2.5 mmol/L, respectively.

The averaged prevalence of diabetes mellitus was 6.1%, increasing with age (age 18-29: 1.9%; 30-39: 2.0%; 40-49: 6.9%; 50-65: 12.1%).

Tijekom godine liječen je u bolnicama 76.871 (13,8%) bolesnik zbog cirkulacijskih bolesti tijekom 108.875 dana. Oko 50% liječenih u neurološkim odjelima liječilo se je zbog cerebrovaskularne bolesti.

Rizični čimbenici hrvatskog pučanstva

Tijekom razdoblja od 1995. do 1997. provedeno je istraživanje rizičnih čimbenika na području Hrvatske u okviru Prvog hrvatskog projekta zdravstva. To je prva randomizirana multicentrična studija kojom je provedeno sveobuhvatno istraživanje u 10.000 ispitanika urbane i ruralne sredine priobalnog i kontinentalnog područja Hrvatske. Terensko istraživanje provedeno je na 30 lokaliteta osječke, zagrebačke, riječke i splitske regije. Konačan uzorak obuhvatio je 5.840 ispitanika obaju spolova u dobi od 18-65 godina. Obradom prikupljenih podataka pomoću anketnog upitnika i uzoraka krvi utvrđena je prevalencija rizičnih čimbenika za hrvatsku populaciju. Rezultati istraživanja pokazali su visoku prevalenciju promjenjivih rizičnih čimbenika.

Prevalencija povišenog krvnog tlaka (RR ≤140/90 mm Hg) iznosi 45%, s većim udjelom u muškaraca (52%) u odnosu na žene (37,9%). Vrijednosti krvnog tlaka značajno rastu s dobi ispitanika.

Ukupno 32,6% odraslih osoba su pušači. Pušenje je više zastupljeno kod muškaraca (34,1%) u odnosu na žene (26,6%).

Tjelesnom aktivnošću aktivno se bavi samo 4,3% žena i 17,1% muškaraca. Kod muškaraca je zastupljena s 4-5 sati na tjedan, a kod žena s 2-4 sata na tjedan.

Prekomjernu tjelesnu težinu (indeks tjelesne mase, ITM 25,0-29,9) ima 41,4% ispitanika, a u skupini debelih (ITM >30.0) je 18,0% ispitanika. Udio pretilih se povećava s dobi kod oba spola, s najvećim udjelom u zagrebačkoj regiji. Značajno je veći udio pretilih muškaraca (21%) u odnosu na žene (15%).

Prosječna (c±SD) koncentracija kolesterola (mmol/L) veća je kod muškaraca (5,81±1,36) nego u žena (5.66±1.29). Ukupno 10% muškaraca ima prosječnu vrijednost kolesterola iznad 7,55 mmol/L, a 10% žena iznad 7,39 mmol/L.

Koncentracije triglicerida (mmol/L) također su veće u muškaraca (2,13±1,69) nego u žena (1,41±0,94). Približno 10% muškaraca ima prosječnu vrijednost triglicerida iznad 3,94 mmol/L, dok jednaki udio žena ima vrijednosti triglicerida iznad 2,5 mmol/L.

Uprosječena prevalencija šećerne bolesti iznosi 6,1%, a u porastu je s dobi ispitanika (18-29 godina 1,9%; 30-39 godina 2,0%; 40-49 godina 6,9%; 50-65 godina 12,1%).

Accordingly, it is concluded that risk factors in the Croatian population have been defined and found to show no major geographical specificities. However, their rates in the general population of Croatia are highly disturbing, as confirmed by the epidemiologic data on cerebrovascular and cardiovascular disease morbidity and mortality. The respective experience from other countries that have achieved favorable results in successful control and prevention of cerebrovascular disease morbidity and mortality is therefore of paramount importance (Table 3).

Table 3.Number of deaths per 100,000 population

	1970	1980	1990	2001
Austria	176.24	150.27	98.85	67.81
Czech Republic	204.65	224.53	202.77	136.13
Croatia	117.5	171.56	176.35	
Hungary	184.52	217.96	177.42	149.07
Slovenia		126.15	92.01	
Poland	55.9	76.96	73.07	103.61
Europe	142.54	158.54	142.55	140.18

Source: Croatian Health Statistics Annals 2001. Zagreb, 2002.

Conclusion

Comprehensive knowledge of the risk factor epidemiology is of utmost importance for the entire health care system. It is highly useful in setting priorities in the organization and financing of the health insurance system and health care system. Therefore, a well defined program of the measures of prevention, early detection and management of cerebrovascular diseases should be designed in order to reduce the related morbidity and mortality rates.

Dakle, možemo ustvrditi da su danas poznati rizični čimbenici hrvatske populacije i da oni nemaju izrazite zemljopisne značajnosti. Međutim, njihov udio u općoj populaciji Hrvatske je više no zabrinjavajući. Upravo epidemiološki podaci o pobolu i smrtnosti od cerebrovaskularnih i kardiovaskularnih bolesti to potvrđuju. Osobito su značajna iskustva drugih zemalja koje u tom području bilježe zapažene rezultate uspješnog suzbijanja pobola i smrtnosti od cerebrovaskularne bolesti (tablica 3.).

Tablica 3. Broj umrlih na 100.000 stanovnika

	1970	1980	1990	2001
Austria	176.24	150.27	98.85	67.81
Czech Republic	204.65	224.53	202.77	136.13
Croatia	117.5	171.56	176.35	
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Poland	55.9	76.96	73.07	103.61
Europe	142.54	158.54	142.55	140.18

Izvor podataka: Hrvatski zdravstveno-statistički ljetopis za 2001. Zagreb, 2002..

Zaključak

Spoznavanje epidemiologije rizičnih čimbenika neobično je važno za cijeli zdravstveni sustav. Ono je značajno za utvrđivanje prioriteta u organizaciji i financiranju sustava zdravstvenog osiguranja i zdravstvene zaštite. Nužno je stoga osmisliti jasan program mjera sprječavanja, ranog otkrivanja i liječenja cerebrovaskularnih bolesti u cilju smanjenja pobola i osobito smrtnosti.

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NEUROSONOLOGIC METHODS IN STROKE DIAGNOSIS
NEUROSONOLOŠKE METODE U DIJAGNOSTICI MOŽDANOG UDARA

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Neurosonology includes both extracranial and intracranial noninvasive cerebrovascular evaluation in stroke patients and high-risk individuals. Due to its noninvasiveness it can be repeated as often as needed, allowing monitoring of the real time cerebral hemodynamics. High-resolution ultrasound provides high-class information on the carotid, vertebral and subclavian artery morphology, giving an insight into the intima-media thickeness (IMT), plaque morphology, echogenicity, plaque surfaces and degree of stenosis. The fine analysis provides information on atherosclerotic or inflammatory vessel wall diseases and on dissection. Duplex ultrasound imaging combines high-resolution gray scale imaging and pulsed Doppler spectral analysis to yield excellent anatomic and physiologic data. The standard diagnostic tool used to examine the extracranial cerebrovascular system is color-coded duplex ultrasound imaging. The superposition of color-flow imaging aids the examiner and interpreter the information of the vessel orientation, anatomic variants, hemodynamic evaluation and various physiologic variants as well as pathologies. The color and power Doppler imaging provides additional information on extracranial brain hemodynamics, making the evaluation more precise and reliable.

Complete appreciation of vessel wall is performed first, using gray-scale imaging with the color turned off. High-resolution ultrasound enables vessel wall evaluation and IMT measurement since the thickening of the IMT is an early marker of atherosclerosis. In earlier studies IMT measurements were performed manually, with the high inter- and intraobserver variability. Nowadays automated computerized systems are available, simplifying reading and improving both accuracy and variability of IMT measurements. There are numerous protocols for evaluation of IMT. Epidemiological studies obtained from different investigations have shown variability in CCA IMT (in 65-year-old males about 0.8-0.73 mm). The results mostly show that males have greater IMT compared to females, and the rate of progression is 0.01 mm *per* year. It seems

Neurosonologija uključuje neinvazivnu procjenu ekstrakranijske i intrakranijske moždane hemodinamike, kako u bolesnika s moždanim udarom, tako i u visokorizičkih osoba. Zbog neinvazivnosti se može ponavljati koliko je god puta potrebno, što omogućava praćenje moždane hemodinamike u živom vremenu. Visokorezolutni ultrazvuk daje vrhunske podatke o morfologiji karotidnih, vertebralnih i potključnih arterija, što omogućava procjenu debljine intime-medije (*intima-media thickness*, IMT), morfologije plaka, ehogenosti, površine plaka i stupnja stenoze. Fina analiza daje podatke o aterosklerotskim ili upalnim promjenama stijenke žile ili o disekciji. Dupleks ultrazvučni prikaz kombinira visokorezolutni prikaz sive skale sa spektralnom frekvencijskom analizom pulsnog doplera kako bi se dobili podrobni podaci o anatomiji i fiziologiji. Standardna oprema u pregledu ekstrakranijskog moždanog krvožilja je obojeni dupleks sustav. Superpozicija bojom kodiranog protoka pomaže ispitivanje i interpretaciju informacija o orijentaciji krvne žile, anatomskim varijantama, procjenu hemodinamike i različitih fizioloških varijanta, kao i procjenu patologije. Boja i sustavi doplerske angiografije omogućavaju dodatne informacije o ekstrakranijskoj moždanoj hemodinamici, što čini procjenu preciznijom i pouzdanijom.

Upotrebom sive skale isključene boje prvo se prikazuje lumen i stijenka žile. Visokorezolutan ultrazvuk omogućava procjenu stijenke žile, mjerenje IMT budući da se njezino zadebljanje pokazalo ranim pokazateljem ateroskleroze. U ranim studijama mjerenje IMT je bilo ručno, s velikom varijabilnošću unutar i između ispitivača. Danas se upotrebljavaju automatski kompjutorizirani sustavi, što pojednostavljuje čitanje, poboljšava točnost i smanjuje varijabilnost mjerenja IMT. Postoje brojni protokoli za procjenu IMT. Iz podataka epidemioloških studija zamijećena je varijabilnost u IMT zajedničke karotidne arterije (ACC) (u 65-godišnjeg muškarca oko 0,8-0,73 mm). Muškarci imaju deblje IMT u usporedbi sa ženama, a debljina raste za 0,01 mm na godinu. Izgleda da svi poznati čimbenici

that all known atherosclerosis risk factors influence IMT, e.g., hypertension, especially the increase in systolic blood pressure, elevated cholesterol and LDL cholesterol, cigarette smoking, diabetes mellitus, some hematologic parameters like fibrinogen levels, fibrinopeptide A, D-dimer, tissue plasminogen activator and plasminogen activator inhibitor, serum copper, and homocysteine level. No correlation was found with the triglyceride levels and HbA1C levels in patients with diabetes mellitus, or with alcohol consumption. An increased IMT was found in patients with coronary heart disease, and individuals with increased IMT were found to be at a greater risk of myocardial infarction, stroke and ischemic stroke. Studies in patients with hiperlipidemia have shown a reduction in IMT with lipid lowering therapy (PLACII, REGRESS). In hypertensive patients ELSA study has shown a reduction of IMT progression in parallel with the risk of stroke and myocardial infarction reduction.

In parallel with vessel wall analysis, the search for plaque is performed. In plaque analysis the morphology, length and echogenicity are evaluated, along with the plaque surface characteristics and the degree of vessel stenosis. Plaques are characterized as being homogeneous or heterogeneous depending on their echogenicity. Homogeneous plaques have a uniform appearance with or without acoustic shadowing. Heterogeneous plaques have a mixture of low, mid and high-level echoes. Low level echoes are the results of lipid, cholesterol, cell debris, necrotic material or interplaque hemorrhage due to rupture of small, vulnerable vessels. The differentiation between these substances is impossible, nevertheless, all of these substances represent unstability of the plaque, with a high risk of embolization or growth. A higher level of echoes usually represents fibrinous material, and high levels of echoes are the result of calcifications. Calcifications can be recognized by total reflection of the ultrasound beam, performing acoustic shadow which makes the analysis of tissue layers under the plaque impossible. These plaques are less harmful and have a lower potential of embolization or smaller growing potential. At the second international consensus meeting, criteria were determined for characterization of carotid plaques. Plaque composition is thus characterized in five steps as follows: 1) uniformly anechogenic plaques with a high risk of stroke; 2) predominantly hypoechoic plaques with hypoechoic areas of more than 50% of plaque structure; 3) predominantly hyperechoic plaques with hypoechoic areas of less than 50% of plaque structure; 4) calcified plaques with the types 2, 3,and 4 of lower stroke risk; and 5) calcified plaques with

rizika ateroskleroze utječu na IMT, kao npr. hipertenzija, te osobito porast sistoličnog krvnog tlaka, povišena razina kolesterola i LDL kolesterola, pušenje, šećerna bolest, neki hematološki parametri kao razina fibrinogena, fibrinopeptida A, D-dimera, tkivni aktivator plazminogena i inhibitor aktivatora plazminogena, razina bakra u serumu i razina homocisteina. Nije nađena povezanost s razinom triglicerida niti s razinom HbA1C u bolesnika sa šećernom bolešću, kao ni s uporabom alkohola. U bolesnika s koronarnom srčanom bolešću nađen je porast IMT koji je bio povezan s porastom rizika za srčani udar, moždani i ishemijski moždani udar. Studije u bolesnika s hiperlipidemijom pokazale su smanjenje IMT tijekom terapije statinima (PLACII, REGRESS). U hipertenzivnih bolesnika studija ELSA je pokazala smanjenje rasta IMT usporedno sa smanjenjem rizika za moždani ili srčani udar.

Usporedno s analizom stijenke žile rutinski se traga za plakovima. U analizi plaka procjenjuje se morfologija, dužina, ehogenosti, značajke površine plaka i stupanj stenoze. Ovisno o ehogenosti, plakovi se opisuju kao homogeni ili heterogeni. Homogeni plakovi se jednoliko prikazuju, a mogu ali ne moraju imati akustičnu sjenu. Heterogeni plakovi imaju mješavinu niske, srednje i visoke razine odjeka. Niske razine odjeka su posljedica masti, kolesterola, staničnog debrisa, nekrotičnog materijala ili krvarenja unutar plaka uslijed pucanja malih, vulnerabilnih žila. Nemoguća je razlika između tih tvari, ali bez obzira na to one sve predstavljaju nestabilnost plaka s visokim rizikom za embolizaciju ili rast plaka. Više razine odjeka obično predstavljaju fibrozni materijal, dok su visoke razine odjeka posljedica kalcifikacija. Kalcifikacije se prepoznaju potpunom refleksijom ultrazvučne zrake, te na taj način tvore akustične sjene koje onemogućuju analizu tkivnih slojeva ispod plaka. Takvi su plakovi manje opasni, imaju nizak potencijal za embolizaciju ili rast plaka. Na Drugom internacionalnom koncenzusnom sastanku definirani su kriteriji za karakterizaciju plakova. Prema sastavu plaka oni se klasificiraju u pet skupina: 1. uniformno anehogeni plakovi s visokim rizikom za nastanak moždanog udara, 2. pretežito hipoehogeni plakovi u kojima hipoehogeni dijelovi zauzimaju više od 50% strukture, 3. pretežito hiperehogeni plakovi u kojima se hipoehogeni dijelovi nalaze u manje od 50% strukture plaka, 4. kalcificirani plakovi, a plakovi tipa 2. ,3., 4. imaju niži rizik za nastanak moždanog udara i 5. kalcificirani plakovi koji tvore akustične sjene koje onemogućuju pregled krvne žile i kod kojih se tek treba ustanoviti rizik za nastanak moždanog udara.

Površina plaka se opisuje kao ravna, nepravilna (katkad je vidljiv prekid endotela ili ulkusi od 0,4-2 mm) ili ulcerira-

acoustic shadow making the vessel lumen evaluation impossible, in which the risk of stroke is still under investigation.

Plaque surface can be characterized as regular, irregular (sometimes disruption of the endothelium is visible, or ulcers of 0.4-2 mm), or ulcerated (with the ulcer depth of >2 mm). Plaque ulcers appear as niche or crater formations on a B-mode image. The imaging in transverse plane is of great help, allowing for differentiation between plaque ulcer and accumulation of more plaques that may appear as irregular surface.

Plaque length and position should be described. Since angiographies are often omitted, surgeon benefits greatly from these additional ultrasound details. The length is also important for the decision on the operation since the length of insonation is the length of the possibility for surgical intervention. Patients with plaques extending to the C2 or intracranial segment are not candidates for surgical intervention. In hemodynamic analysis the plaque length, position and composition influences velocity measurement.

The possibility of assessment of the plaque stability may be offered by three- and four-dimensional ultrasound.

The benefit of carotid endarterectomy in stroke prevention in advanced carotid stenosis was proved in large studies (ECST and NASCET). They were based on angiographic findings, although using different methods of stenosis measurement. If noninvasive imaging is to replace angiography, the exact relationship between the degree of stenosis measured by ultrasonographic technique and that measured by angiography must be accurately defined. The previously reported studies evaluated sensitivity and specificity of different criteria used for assessment of the degree of carotid stenosis. While in some investigations the peak systolic velocity (PSV) in ICA was found to be the best single velocity parameter for quantifying a >70% stenosis, in others it was the PSV ratio in ICA and CCA. The more so, color Doppler flow imaging enabled visualization of pseudo-occlusion, thus being superior to angiography. The application of the same ultrasonographic diagnostic criterion of PSV at two ultrasonographic laboratories using similar equipment showed different sensitivity and specificity in grading of carotid stenosis. A higher sensitivity of ultrasound screening was achieved by use of diagnostic criteria specific to each laboratory. The combination of different criteria used at our laboratory to estimate the degree of carotid stenosis has been published. Grading was made for clinical purposes, since mild stenosis does not require frequent controls, moderate stenosis na (s ulkusima većim od 2 mm). Ulkusi plaka se prikazuju kao niše ili formacije kratera na B-mod slici. Poprečni prikaz će omogućiti razlikovanje ulkusa plaka od nakupine više plakova koji se tada mogu prikazivati kao neravna površina u longitudinalnom prikazu.

U izvještaju se opisuje dužina i položaj plaka. Budući da u većine bolesnika neće biti učinjena angiografija, vaskularnim kirurzima će takve dodatne informacije biti od pomoći. Dužina plaka je važna u procjeni odluke za operaciju, budući da je dužina insonacije ujedno i dužina do koje je dostupan operacijski zahvat. Bolesnici s plakovima koji se protežu u C2 ili intrakranijski segment nisu kandidati za kiruršku intervenciju. U analizi hemodinamike dužina plaka, položaj i sadržaj utječu na izmjerenu brzinu u stenoziranom području.

Tro- i četverodimenzionalni ultrazvuk može pružiti dodatne informaciji u procjeni stabilnosti plaka.

Uspješnost karotidne endarterektomije u sekundarnoj prevenciji moždanog udara je dokazana u velikim studijama (ECST, NASCET). One su bile zasnovane na nalazu angiografije, iako su upotrebljavale različite metode mjerenja stenoze. Budući da neinvazivan prikaz treba zamijeniti angiografiju, potrebno je točno definirati kriterije mjerenja karotidne stenoze u usporedbi s angiografijom. Prethodne su studije uspoređivale osjetljivost i specifičnost različitih kriterija u procjeni razine karotidne stenoze. Dok su neka istraživanja pokazala maksimalnu sistoličnu brzinu u unutarnoj karotidnoj arteriji (ACI) kao najbolji pojedinačni parametar brzine za određivanje stenoze veće od 70%, u drugim istraživanjima je to bio odnos maksimalnih sistoličnih brzina u unutarnjoj i zajedničkoj karotidnoj arteriji. Neka istraživanja su pokazala i da je bojom kodirana doplerska sonografija osjetljivija metoda za otkrivanje pseudookluzije, čak bolja od angiografije. Primjena ultrazvučnih dijagnostičkih kriterija maksimalnih sistoličnih brzina u dva ultrazvučna laboratorija slične opreme je pokazala različitu osjetljivost i specifičnost u procjeni karotidne stenoze. Postignuta je veća osjetljivost ultrazvučnog pretraživanja kada su bili upotrebljeni specifični dijagnostički kriteriji za svaki pojedini laboratorij. Objavili smo kombinaciju različitih kriterija našeg laboratorija kako bismo procijenili karotidnu stenozu. Stupnjevanje je bilo učinjeno u kliničke svrhe, budući da se blaže stenoze ne trebaju često kontrolirati, češće se kontroliraju umjerene stenoze, dok su značajne stenoze kandidati za kiruršku intervenciju. Bolesnici s karotidnom okluzijom se prate. Takvi su rezultati pokazali visoku korelaciju između angiografije i ultrasonografije u procjeni različitih stupnjeva karotidne stenoze. Ultrazvuk je bio osjetljiviji u procjeni značajne karotidne stenoze

has to be controlled more frequent, and advanced stenosis patients are candidates for surgical intervention. The carotid occlusion patients are monitored. These results showed a high correlation between angiography and ultrasonography in detecting various degrees of carotid stenosis. Ultrasound was more sensitive in detecting the category of severe stenosis (near occlusion, pseudo-occlusion), as also demonstrated in other studies. Such a combination of various ultrsonographic parameters proved to be sensitive for the detection of various degrees of carotid stenosis, with a very high specificity and yielding high positive predictive values for such classification.

Although one fourth of ischemic strokes are related to the vertebrobasilar territory, the investigations of vertebral arteries have not become so popular. The reason is the technical problem due to the anatomic position of the vessels, a low rate of vertebral endarterectomies, and a low rate of vertebral stenosis as a cause of vertebrobasilar stroke. Vertebral occlusions may clinically present as a TIA, or a mild stroke. Vertebral color Doppler imaging may show physiologic variations in vertebral arteries such as asymmetry in diameter, hypoplasia or variation in the positioning in the extracranial part. Doppler parameters may indicate variation of the intracranial part. Superposition of color coded flow (in color and in power mode) enabled better visualization of vertebral artery pathology such as stenosis, occlusion or dissection.

Vasculitis of the nervous system includes a group of disorders characterized by the histologic feature of inflammation of blood vessels. The diagnosis is suspected on clinical presentation, and confirmed by signs of inflammation obtained by laboratory analysis or biopsy. Doppler sonography may help in noninvasive visualization of the disease, if the disease is localized in a segment that is accessible to the ultrasound investigation, as in giant cell arteritis that affects mostly branches of the aortic arch, in cranial arteritis or Takayasu's arteritis. Takayasu's arteritis is affecting the branches of the aorta, brachiocephalic trunk, ostium of the common carotid artery or subclavian artery, or renal artery (which results in hypertension). According to localization, good visualization of the lesions by color Doppler is expected. Advanced stenosis of the brachiocephalic trunk cannot be always directly visualized, but attenuated, changed spectra in both the carotid and subclavian arteries can be recorded. Mural thickening of the common carotid arteries can be easily seen. Advanced stenosis or occlusion of the subclavian arteries can be sometimes directly seen, and more information can be additionally obtained by visualization of vertebral arteries. Ad-

(gotovo okluzija, pseudookluzija), što je već bilo zamijećeno u drugim studijama. Takva se kombinacija ultrazvučnih parametara pokazala osjetljivom u otkrivanju različitih stupnjeva karotidne stenoze, uz vrlo visoku specifičnost, što je dovelo do visoke pozitivne prediktivne vrijednosti za takvu klasifikaciju.

Iako je četvrtina ishemijskih moždanih udara smještena u vertebrobazilarnom teritoriju, istraživanja vertebralnih arterija nisu postala u toj mjeri popularna. Razlog je tehnički problem zbog anatomskog položaja žila, niske razine vertebralih endarterektomija i niske razine vertebralnih stenoza kao uzroka vertebrobazilanog moždanog udara. Vertebralna okluzija se može klinički prikazati kao prolazni ishemijski napadaj (TIA) ili blagi moždani udar. Obojeni dopler vertebralnih arterija može pokazati fiziološke varijacije vertebralnih arterija kao asimetrije dijametra, hipoplaziju ili varijacije položaja u ekstrakranijskom dijelu. Doplerski parametri mogu ukazivati na varijacije intrakranijskog dijela. Superpozicija bojom kodiranog protoka (u boji ili doplerskoj angiografiji) omogućava bolji prikaz patoloških promjena vertebralnih arterija kao stenoze, okluzije ili disekcije.

Vaskulitis živčanog sustava uključuje skupinu poremećaja koji su obilježeni histološkim značajkama upale krvnih žila. Na osnovi kliničke prezentacije postavlja se sumnja na dijagnozu, a potvrđuje se znacima upale koji se otkivaju laboratorijskom analizom ili biopsijom. Doplerska sonografija može pomoći u neinvazivnoj vizualizaciji bolesti ako je lokalizacija bolesti prisutna u segmentu koji je dostupan ultrazvučnoj pretrazi, kao u arteritisu orijaških stanica koji najčešće zahvaća grane luka aorte, u kranijskom arteritisu i Takayasuovu arteritisu. Takayasuov arteritis zahvaća grane luka aorte, trunkus brahiocefalikus, ušće zajedničke karotidne arterije, potključne ili bubrežne arterije (što dovodi do hipertenzije). U skladu s lokalizacijom očekuje se dobar prikaz lezije obojenim doplerom. Katkada se ne može izravno vidjeti značajna stenoza brahiocefaličnog trunkusa, ali se bilježi promijenjeni, atenuirani hemodinamski spektar u karotidnoj i potključnoj arteriji. Zadebljanje stijenke zajedničke karotidne arterije se lagano vidi. Značajna stenoza ili okluzija potključne arterije se katkada dobro prikazuje, a dodatne informacije se dodatno postižu prikazom vertebralnih arterija. Značajna okluzivna bolest potključne arterije ispod polazišta vertebralne arterije dovodi do kompenzacijskih promjena hemodinamike vertebralne arterije, pojave koja se naziva djelomičan ili potpun sindrom krađe krvi potključne arterije. Perfuzija ruke je potpomognuta iz suprotne potključne arterije preko kontralateralne u ipsilateralnu vertebralnu

vanced occlusive disease of subclavian artery before the origin of vertebral artery lead to compensatory changed hemodynamics in vertebral artery, the phenomenon being known as partial or complete subclavian steal syndrome. Arm perfusion is supported from the other subclavian artery *via* contralateral and then ipsilateral vertebral artery. Therefore, the hemodynamics is partially or completely inversed in ipsilateral vertebral artery and accelerated in the contralateral one.

Vasculitis affecting smaller arteries may alter intracranial hemodynamics, which can be measured as impaired vasoreactivity as a marker of smaller vessel involvement.

Moyamoya disease is a clinical entity of unknown etiology, occurring mainly in Japanese children, rarely in Caucasians, and characterized by angiographic findings of bilateral occlusion at the terminal portions of the internal carotid artery together with a vascular network at the base of the brain. As a syndrome in other disease it leads to slowly progressive basal cerebral artery stenosis. In extracranial carotid arteries indirect signs of intracranial occlusive disease can be detected.

Fibromuscular dysplasia is a nonatheromatous arterial disease of unknown etiology characterized by segmental narrowing of intermediate-sized arteries in many areas of the body. Proliferations of different artery layers are leading to narrowing, dissections and aneurysm formation. Complete occlusion of the internal carotid or vertebral artery may develop, leading to stroke. Color-coded Doppler sonography reveals the same findings as angiography, as a string-pearl formation, unifocal or multifocal tubular stenosis, diverticulum-like or aneurysmal dilatation. Asymptomatic stenotic process is usually localized in C2 portion, while the symptomatic is usually found at bifurcation, leading to ischemic symptoms. Such vessels are candidates for dissection, although dissection may appear in trauma, or without known risk factors.

Dissections may appear as different findings in color-coded Doppler mode. When extending from the aortic arch, double lumina can be seen. Bifurcation stenosis may dissect leading to the formation of color-coded flow in the plaque base. In younger persons dissections are usually affecting distal parts of the internal carotid arteries or vertebral arteries. Hypoechoic stenosis of the vessels in distal parts can be seen, or when located intracranially and leading to complete occlusion, then indirect signs of distal occlusions are present. Such signs include dampened flow with a high resistance pattern, and possible inversed hemodynamics during diastole.

Transcranial Doppler (TCD) was introduced in clinical use in 1982, and proved to be a noninvasive, fast and

arteriju. Stoga se hemodinamika djelomice ili potpuno okreće u ipsilateralnoj vertebralnoj arteriji, dok je u kontralateralnoj ubrzana.

Vaskulitis koji zahvaća manje arterije može utjecati na intrakranijsku hemodinamiku koja može biti promijenjene vazoreaktivnosti kao biljeg zahvaćanja manjih žila.

Bolest *moyamoya* je klinički entitet nepoznate etiologije koji se javlja češće u djece u Japanu, rjeđe u bijelaca, a obilježena je angiografskim nalazom bilateralnih okluzija terminalnih dijelova unutarnje karotidne arterije uz razvoj kolateralne vaskularne mreže baze mozga. Kao sindrom u drugim bolestima dovodi do sporo progresivne stenoze bazalnih moždanih arterija. U ekstrakranijskim karotidnim arterijama se bilježe neizravni znaci intrakranijske okluzivne bolesti.

Fibromuskularna displazija je neateromska arterijska bolest nepoznate etiologije koja je obilježena segmentnim sužavanjima arterija srednje veličine u različitim dijelovima tijela. Proliferacija različitih arterijskih slojeva dovodi do sužavanja, disekcije i stvaranja aneurizme. Može nastati potpuna okluzija unutarnje karotidne ili vertebralnih arterija, što dovodi do nastanka moždanog udara. Bojom kodirana doplerska sonografija pokazuje isti nalaz kao angiografija, vidljiva je formacija poput žice ili niske bisera, unifokalne ili multifokalne tubularne stenoze ili proširenja poput divertikula ili aneurizme. Asimptomatski stenotički proces obično je lokaliziran u segmentu C2, a ako je bolest lokalizirana u bifurkaciji češće dovodi do pojave ishemijske simptomatologije. Takve krvne žile su podložne disekciji, iako se disekcija može javiti tijekom traume s ili bez poznatih čimbenika rizika.

Disekcija može različito izgledati na slikama obojenog doplera. Kada se proteže iz luka aorte može se vidjeti dvostruki lumen. Stenoze u području bifurkacije mogu disecirati i tvoriti bojom kodirani protok u bazi plaka. U mlađih osoba disekcija obično zahvaća distalne dijelove unutarnjih karotidnih ili vertebralnih arterija. Tada se mogu vidjeti sužavanja lumena žila hipoehogenom masom u distalnom dijelu, a ako se protežu intrakranijski i dovode do potpune okluzije, tada su prisutni neizravni znaci distalne okluzije. Takvi znakovi uključuju izrazitu atenuaciju protoka, odgođene sistolične akceleracije protoka, visoku rezistenciju u hemodinamskom spektru i katkad obrnutu hemodinamiku tijekom dijastole.

Godine 1982. uveden je u kliničku uporabu transkranijski doplер (TCD) i pokazao se je neinvazivnom, brzom i točnom dijagnostičkom metodom u procjeni moždane hemodinamike. Glavna je prednost TCD mogućnost vremenske rezolucije mjerenja. Takva tehnika omogućava praćenje i razumijevanje promjena moždane cirkulacije u

exact diagnostic tool for the evaluation of cerebral hemodynamics. One of the advantages of TCD is the possibility of time resolution of the measurements. This technique allows for monitoring and thus understanding changes in the cerebral circulation under normal and pathologic conditions. Relative changes in cerebral hemodynamics can be measured objectively, and as long and often as necessary. This quality makes TCD irreplaceable in the clinical follow-up of patients and an attractive tool for dealing with scientific issues. The first application was detection and monitoring of cerebral vasospasam, invented by Rune Aaslid, and ever since it has been extensively employed in a variety of clinical settings. The major advantage of TCD application is the revealing and screening patients with acute vascular pathology such as intracranial blood vessel occlusive disease, to monitor and enhance rt-TPA thrombolysis recanalization, evaluation of intracranial collateral capacity and redistribution of hemodynamics in extra- or intracranial occlusive disease, hemodynamic evaluation of tandem lesions, screening for vascular malformations, and evaluation of feeding arteries, monitoring of vasospasm, brain edema and brain death, intraoprative monitoring, etc. Recent TCD modalities enable estimation of cerebral vasoreactivity, "brain stress test" and cerebral autoregulation by analyzing cerebral microcirculatory responses after stimulation test such as CO2 reactivity, acetazolamide or functional tests by cognitive tasks. Introduction of new software has enabled detection of cerebral microembolic signals. The union of duplex scan image and pulsed Doppler has enabled imaging of the brain parenchyma with superposition of color-coded Doppler flow. By this application the brain hemodynamic evaluation has become more reliable than before. Yet, TCD requires operator's skill, experience and good mental imaging of the brain vessels.

Various physiologic conditions may influence TCD findings, e.g., common anatomic variations of the circle of Willis and vertebrobasilar system. Therefore the missing signal (especially A1 or P1), asymmetry should not be interpreted as abnormal. The blood flow velocities decrease with age, hypertension increases mean flow velocities with increased flow pulsatility. Hypercapnia increases mean flow velocities and decreases flow pulsatility, whereas hyperventilation decreases mean flow velocities and increases pulsatility. Various factors including extra- or intracranial stenosis or occlusions, or changed downstream circulatory conditions like increased intracranial pressure, or dilated or spastic resistance vessels determine the waveform patterns. Changes of blood parameters alter blood flow velocinormalnim i patološkim uvjetima. Relativne promjene moždane hemodinamike mogu se objektivno mjeriti koliko je god dugo potrebno. Ova kvaliteta čini TCD nezamjenjivom metodom u kliničkom praćenju bolesnika i primamljivom tehnikom u znanstvenim istraživanjima. Prva je primjena bila otkrivanje i praćenje moždanog vazospazma, a prvi ju je primijenio Rune Aaslid i otada se naširoko primjenjuje u različitim kliničkim uvjetima. Glavna primjena TCD je u otkrivanju i praćenju bolesnika s akutnom vaskularnom patologijom kao okluzivnom bolesti intrakranijskih krvnih žila, praćenju i pospješivanju rekanalizacije upotrebom tkivnog aktivatora plazminogena, procjena intrakranijskog kolateralnog kapaciteta i redistribucije hemodinamike u ekstra- ili intrakranijskoj okluzivnoj bolesti, hemodinamska procjena tandemskih lezija, potraga za vaskularnim malformacijama i evaluacija žila hraniteljica, praćenje vazospazma, moždanog edema i moždane smrti, intraoperacijsko praćenje itd. Novije mogućnosti TCD omogućavaju procjenu moždane vazoreaktivnosti, "stres testovi mozga" i moždana autoregulacija analizom cerebralnog mikrocirkulacijskog odgovora na podražaje kao reaktivnost na ugljični dioksid, acetazolamid ili funkcijske testove kognitivnom stimulacijom. Primjena novih programa omogućava otkrivanje cerebralnih mikroembolijskih signala. Sustavi koji imaju ujedinjeni dupleks prikaz i pulsni dopler omogućavaju prikaz moždanog parenhima uza superpoziciju bojom kodiranog protoka. Na taj je način procjena moždane hemodinamike pouzdanija nego ranije. Ipak TCD zahtijeva spretnost i iskustvo izvođača i dobru mentalnu orijentaciju o moždanom krvožilju.

Brojni fiziološki uvjeti mogu utjecati na nalaz TCD, kao česte anatomske varijacije Willisova kruga i vertebrobazilarnog sustava. Stoga, ako nedostaje neki signal (osobito A1 ili P1), asimetrija se ne tumači kao abnormalna. Brzine strujanja krvi se smanjuju s dobi, hipertenzija povisuje srednje brzine strujanja uz porast pulsatilnosti protoka. Hiperkapnija povisuje srednje brzine protoka i smanjuje pulsatilnost, dok hiperventilacija snizuje srednje brzine protoka i povisuje pulsatilnost. Različiti čimbenici utječu na izgled signature vala, a uključuju ekstra- ili intrakranijsku stenozu ili okluziju, promijenjene cirkulacijske uvjete nizvodno kao porast intrakranijskog tlaka ili proširene ili spastične rezistentne žile. Promjene krvnih parametara utječu na brzine te tako anemija povisuje brzine strujanja krvi, dok porast viskoznosti u policitemiji ili povišenim razinama fibrinogena snizuje brzine strujanja krvi.

Uz procjenu intrakranijskih fizioloških uvjeta mogu se ustanoviti i locirati patološki uvjeti kao stenoza ili okluzija. TCD može predvidjeti ishod moždanog udara ovisno o

ties, anemia increases blood flow velocities, whereas increased viscosity in polycythemia or increased fibrinogen levels lowers blood flow velocities.

Besides evaluation of intracranial physiologic conditions, pathologic conditions like stenosis or occlusion can be seen and located. TCD may predict stroke outcome depending on the localization of the intracranial vessel occlusion. Recanalization of the occluded or stenosed vessel can be monitored. Diagnostic ultrasound in combination with the tissue plasminogen activator (tPA) enhances tPA-induced recanalization thus improving outcome.

In hemorrhagic stroke TCD provides information on intracranial pathology like vascular malformations or development of vasospasm. Due to transportability and noninvasiveness it can be repeated many times, thus enabling monitoring of the time course of vasospasm or intracranial pressure increase. The development of cerebral circulatory arrest can be monitored as part of brain death protocol.

Likewise the evaluation of normal hemodynamics, transcranial color-coded Doppler (TCCD) sonography provides more reliable information in the assessment of intracranial pathology. The color-coded flow is superimposed on gray scale image of the brain parenchyma using several brain markers for orientation. Switching the color on, the color-coded flow images through the vessels of the circle of Willis are displayed. Placing the sample volume on a defined color-coded signal, the hemodynamics of the desired segment is displayed. The accuracy of the intracranial hemodynamic analysis is more reliable. By placing the transducer suboccipitally, under the foramen magnus, the vertebrobasilar system is displayed. Due to the tortuosity of the vessels, an adequate image of the basilar artery origin and course is rarely obtained.

Vascular malformation can be visualized by means of TCCD, and brain-feeding arteries can be assessed. Aneurysms can be displayed as an additional color-coded structure adjacent to the artery, with a characteristic color-coded flow pattern. In subarachnoid hemorrhage the vessels will be thinny due to vasospasm. Vasospasm of the cerebral vessels refers to a transient contraction of the intracranial arteries, which can occur in a variety of disorders affecting the central nervous system and can produce transient or permanent neurologic dysfunction by inducing cerebral ischemia. The most common clinical setting is following spontaneous subarachnoid hemorrhage, frequently secondary to rupture of intracranial aneurysms, but may also follow brain trauma, meningitis and preeclampsia. Vasospasm is the primary cause of delayed ischemic neurologic deficit and mortality. Therefore it is important

lokalizaciji intrakranijske okluzije žile. Može se pratiti rekanalizacija okludirane ili stenozirane žile. Dijagnostički ultrazvuk u kombinaciji s tkivnim aktivatorom plazminogena (tPA) pospješuje tPA-om izazvanu rekanalizaciju i poboljšava ishod u bolesnika.

U hemoragičnom moždanom udaru TCD pruža informacije o intrakranijskoj patologiji, kao o prisutnosti vaskularnih malformacija ili razvoju vazospazma. Budući da je prijenosan i neinvazivan, može se više puta ponavljati, što omogućava praćenje tijeka vazospazma ili porasta intrakranijskog tlaka. Moguće je pratiti razvoj cerebralnog cirkulacijskog aresta u dijagnostici moždane smrti.

Transkranijska bojom kodirana doplerska (TCCD) sonografija pruža pouzdanije informacije u procjeni intrakranijske normalne i patološke hemodinamike. Bojom kodirani protok se superponira na sivu skalu prikaza moždanog parenhima, gdje se rabe dijelovi mozga kao orijentacijske točke. Uključivanjem boje prikazuje se bojom kodirani protok u žilama Willisova kruga. Kada se osjetljiv uzorak postavi na definirani bojom kodirani signal, prikazuje se hemodinamika u željenom segmentu. Točnost analize prikazane intrakranijske hemodinamike je veća. Postavljanjem sonde subokcipitalno, ispod velikog otvora, prikazuje se vertebrobazilarni sustav. Zbog vijugavosti žila rijetko se primjereno prikaže polazište i tijek bazilarne arterije.

Upotrebom TCCD mogu se prikazati vaskularne malformacije i procijeniti žile hraniteljice. Aneurizme se prikazuju kao dodatna struktura boje uz arteriju, uz znakovito bojenje kolorom kodiranog protoka. U subarahnoidnom krvarenju žile su uske zbog vazospazma. Vazospazam je prolazna kontrakcija moždanih krvnih žila koja nastaje u različitim bolestima koje zahvaćaju središnji živčani sustav, uzrokuje moždanu ishemiju i može dovesti do prolazne ili trajne neurološke disfunkcije. Najčešće nastaje nakon spontanog subarahnoidnog krvarenja, često nakon rupture intrakranijske aneurizme, ali može nastati i nakon moždane traume, u sklopu meningitisa ili eklampsije. Vazospazam je primarni uzrok odgođenih ishemijskih neuroloških deficita i smrtnosti. Stoga je važno imati mogućnost njegova neinvazivnog otkrivanja i praćenja kako bi se moglo primijeniti učinkovito liječenje. TCD je pouzdana metoda u dijagnostici moždanog vazospazma mjerenjem porasta brzina strujanja krvi u bazalnih moždanim arterijama. Odnos ACM/ACI se može izračunati kako bi se isključila hiperperfuzija.

Doplerski spektar sadrži informacije koje se odnose na intenzitet ili količinu zvuka koja se reflektira prema sondi. To je odnos broja crvenih krvnih stanica i označava količinu krvi unutar osjetljivog uzroka. Intenzitet reflek-

to have a noninvasive possibility for its detection and monitoring, so that effective treatment can be used. TCD is a reliable method for detecting cerebral vasospasm by measuring the increased blood flow velocities in basal cerebral arteries. The MCA/ICA ratio can be calculated to exclude hyperperfusion.

Doppler spectrum contains information regarding the intensity or amount of sound that is reflected back to the transducer. It is in proportion to the number of red blood cells and indicates the amount of blood in the sample volume. The intensity of the reflected sound at a particular frequency depends on the number of red blood cells moving at a particular velocity. The signal power of each velocity component can be coded in a color or gray scale on a computer display using the spectrum analysis technique. An embolus moving through the sample volume increases the amount of ultrasound being reflected back to the transducer, so this hyperintensive transient signal increase (HITS) in the Doppler spectrum corresponds to the microembolic signal (MES) as the embolic particle passes through the cerebral circulation. MES are more frequently detected when retesting a suspected individual on different days, or on prolonged monitoring. The accurate and reliable characterization of embolus size and composition is not yet possible using current technology. The ability to detect emboli is hampered by several factors including equipment characteristics. Embolus size and echogenicity determine the intensity of the signal. MES can be found more frequently in patients with symptomatic than in those with asymptomatic carotid stenosis. Most MES are asymptomatic, but are still believed to be a marker of the risk of ischemic events. Similar are data for patients with atrial fibrillation, prosthetic heart valves, and mural thrombus in the left atrium. MES detection can be used to localize an embolic source and to identify high-risk patients with carotid or arterial sources of embolism, to monitor patients during invasive procedures or operations, and to assess the effect of antithrombotic or anticoagulant treatment. The standardization of the equipment, methodology, and methods for analysis and interpretation (to lessen inter- and intraobserver variability and semi-automatic embolus detection algorithms) is required to obtain high report sensitivity and specificity.

Paradoxical embolism may occur *via* a patent foramen ovale or presence of an atrial septal aneurysm. Bubble test is performed by injection of saline containing air bubbles or echo-contrast enhancing agents into the cubital vein. TCD registers the HITS appearing in the left MCA. They may appear as single emboli, multiple emboli, shower without curtain, and curtain of emboli. The sensitivity of contiranog zvuka na određenoj frekvenciji ovisi o broju crvenih krvnih stanica koje se kreću određenom brzinom. Signal snage svake komponente brzine se može kodirati u boji ili intenzitetom sive skale na zaslonu računala, upotrebom tehnike spektralne analize. Embolus koji prolazi kroz osjetljiv uzorak povećava količinu ultrazvuka koji se reflektira prema sondi, tako da hiperintenzivno prolazno povećanje signala (*high intensity transient signal*, HITS) doplerovog spektra odgovara mikroembolijskom signalu (MES) kada čestica embolijskog materijala prolazi kroz moždanu cirkulaciju. Veća je vjerojatnost otkrivanja MES kada se ponavljano, u više dana, testira pojedinac kod kojeg se očekuje njegova pojava ili kod produženog snimanja. Primjenom sadašnje tehnologije zasad nije moguće točno i pouzdano odrediti veličinu embolusa i njegov sastav. Nekoliko čimbenika, uključujući značajke opreme, utječu na mogućnost otkrivanja embolija. Veličina embolusa i ehogenost određuju intenzitet signala. Češće se otkrivaju MES u bolesnika sa simptomatskom nego u bolesnika s asimptomatskom karotidnom stenozom. Većinom su MES asimptomatski, ali se ipak vjeruje da predstavljaju biljeg rizika za nastanak ishemijskih događaja. Slični su podaci za bolesnike s atrijskom fibrilacijom, umjetnim srčanim valvulama, muralnim trombom u lijevom atriju. Otkrivanje MES se može upotrijebiti kako bi se lokalizirao izvor embolija i identificirali visoko rizični bolesnici s karotidnim ili arterijskim izvorom embolija, pratilo bolesnike za vrijeme invazivnih postupaka ili operacije i procijenio učinak antitrombotske ili antikoagulantne terapije. Potrebna je standardizacija opreme, metodologije i metode za analizu i interpretaciju (i u manjoj mjeri varijabilnost unutar i između ispitivača i algoritam poluautomatskog otkrivanja embolija), kako bi se postigla visoka osjetljivost i specifičnost nalaza.

Paradoksični embolizam može nastati preko otvorenog foramena ovale ili prisutnosti atrijske septalne aneurizme. Primjenjuje se test mjehurića tako da se injicira fiziološka otopina koja sadrži zračne mjehuriće ili eho-kontrastno sredstvo u kubitalnu venu. Pomoću TCD bilježe se HITS koji se pojavljuju u lijevoj srednjoj moždanoj arteriji. Može se javiti jedan embolus, više embolija, tuš emoblija bez zastora ili zastor pun embolusa. Senzitivnost kontrastnog TCD se kreće od 70% do 100% uza specifičnost koja prelazi 95% u otkrivanju desno-lijevih srčanih ili plućnih arteriovenskih komunikacija. Rutinsko izvođenje Valsalvina manevra za vrijeme testa povećava osjetljivost i specifičnost.

Moždana vazoreaktivnost je fiziološki zaštitni mehanizam koji čuva mozak od oštećenja tako što održava njegovu opskrbu krvlju stalnom. Cerebralna arterijska autoreg-

trast TCD ranges between 70% and 100%, with the specificity exceeding 95% in detecting right to left cardiac or pulmonary arteriovenous shunts. The routine performance of Valsalva maneuver during the test can improve sensitivity and specificity.

Cerebral vasoreactivity is a psychological protective mechanism that prevents brain damage by keeping stable blood flow supply. Cerebral arterial autoregulation is accomplished by resistance changes that occur at the level of smaller cerebral arteries, while the basal cerebral arteries remain constant in diameter during moderate pressure fluctuations. Cerebral vasoreactivity could be estimated by measuring mean blood flow velocity changes during cerebral vessel stimulation tests by TCD. They all are based on the biophysiology of vessel wall responsiveness. The best known are CO2 and acetazolamide tests, which can be combined with TCD. These tests provoke changes in cerebral arteriolar diameters, influencing cerebral blood flow changes. Induced hypercapnia strongly stimulates vasodilatation of cerebral arterioles, lowers peripheral blood pressure, and increases blood flow velocities. In patients with exhausted cerebral vasomotor reaction, the resistance bed is dilated at baseline and no further dilatation is possible. They express impaired cerebral vasoreactivity to vasodilator stimuli. Such patients are at an increased risk of development of cerebrovascular ischemic event. In patients with severe extracranial internal carotid disease, diminished vasomotor reactivity has been associated with an increased risk of stroke, and spontaneously improved following endarterectomy.

Cerebrovascular ultrasonography has shown an almost exponential growth over the last decades. Many ultrasound techniques are available for routine noninvasive examination of extracranial arteries in the detection and quantification of stenosis, evaluation of plaque stability, diagnosis and follow up of dissections, evaluation of intracranial hemodynamics and redistribution in the presence of collateral flow. Applied with rt-TPA, it enhances thrombolysis. New software enables noninvasive embolus detection and functional imaging. All this enables complete diagnosis of stroke patients and of individuals at stroke risk. The great advantage is that the methods are easy, reliable, noninvasive, and can be repeated as much as needed. The equipment is small and transportable, enabling evaluation at patient bedside.

ulacija je praćena promjenama rezistencije na razini malih moždanih arterija, dok bazalne cerebralne arterije ostaju iste širine promjera za vrijeme umjerenih promjena krvnog tlaka. Moždana se vazoreaktivnost može procijeniti tako da se pomoću TCD mjere promjene srednjih brzina strujanja krvi za vrijeme testa stimulacije moždanih žila. Svi su zasnovani na biofiziologiji odgovora stijenke žila. Najpoznatiji je test stimulacije ugljičnim dioksidom ili acetazolamidom u kombinaciji s TCD. Ti testovi uzrokuju promjene promjera moždanih arteriola i na taj način mijenjaju moždani protok krvi. Inducirana hiperkapnija snažno stimulira vazodilataciju moždanih arteriola, snizuje periferni krvni tlak i povećava brzine strujanja krvi. U bolesnika s iscrpljenom moždanom vazomotornom reakcijom rezistentne žile su osnovno proširene do najveće moguće mjere i nije moguća daljnja dilatacija. Oni pokazuju poremećen cerebralni vazoreaktivni odgovor na vazodilatacijske podražaje. Takvi su bolesnici pod povećanim rizikom za razvoj cerebrovaskularnog ishemijskog događaja. U bolesnika sa značajnom stenozom unutarnje karotidne arterije smanjena vazomotorna reaktivnost je povezana s povećanim rizikom za nastanak moždanog udara i spontano se poboljšava nakon endarterektomije.

Ultrasonografija moždanih krvnih žila je posljednjih desetljeća doživjela eksponencijalni rast. Dostupne su mnoge ultrazvučne tehnike za rutinsko neinvazivno ispitivanje ekstrakranijskih arterija u otkrivanju i kvantifikaciji stenoze, procjeni stabilnosti plaka, dijagnozi i praćenju disekcija, procjeni intrakranijske hemodinamike i preraspodjeli hemodinamike u prisutnosti kolateralnog protoka. Primijenjena uz tkivni aktivator plazminogena pospješuje trombolizu. Noviji programi omogućavaju neinvazivno otkrivanje embolijskih signala i funkcionalni prikaz. Sve to omogućava potpunu dijagnostiku bolesnika s moždanim udarom i pojedinaca pod rizikom za njegov nastanak. Velika je prednosti metoda to što su jednostavne, pouzdane, neinvazivne i mogu se ponavljati koliko je god puta potrebno. Oprema je mala i prijenosna, što omogućava procjenu uz krevet bolesnika.

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NEUROPHYSIOLOGIC METHODS IN STROKE DIAGNOSIS
NEUROFIZIOLOŠKE METODE U DIJAGNOSTICI MOŽDANOG UDARA

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Clinical neurophysiology methods are commonly defined as methods for recording the bioelectrical cellular activity. In case of cerebral pathology, electroencephalography (EEG) and methods derived from it have so far been dominant techniques. With the same purpose different variations of evoked potentials (EP), sensory and motor, can be applied. A common feature of all of these techniques is visual presentation of the spatially and temporarily summed neuronal activity, which is enabled by specific structural and functional organization of the brain. Concerning the origin of EEG activity, great populations of parallelly-oriented neurons make possible the formation of transient electrical gradients, their voltages being sufficient to be recorded on the scalp surface. In comparison to neuroimaging methods, the main advantage of the neurophysiologic methods is their high temporal resolution that cannot be reached even by the last generations of the functional magnetic resonance imaging (fMRI), as well as their promptness by which the electrophysiologic parameters appear during the pathophysiologic brain processes. However, the common characteristic of the registered neurophysiologic parameters is that they are the result of a complex cerebral integration of the spatially remote neural networks. Consequently, the implication of this is a considerably weaker spatial resolution if compared to the standard neuroimaging techniques.

In the routine diagnosis of stroke, which can be defined by a sudden appearance of the neurologic deficit that may be attributable to focal vascular pathology[1], in the majority of cases the neurophysiologic methods are not indicated. Neither by the localization value, nor by the specifity of the findings can they replace contemporary neuroimaging techniques. In addition to this, no direct conclusion regarding vascular pathology can be made. Nevertheless, there are situations in the stroke diagnosis when neurophysiologic methods have the advantage over the neuroimaging ones. For instance, this is the situation when the ischemic lesion has not yet become apparent on the computerized tomography images (CT). In contrast to this, EEG shows abnormalities almost simultaneously with the

Kliničke neurofiziološke metode često se definiraju kao metode za registriranje bioelektrične stanične aktivnosti. U slučaju moždane patologije dosad su prevladavale elektroencefalografija (EEG) i iz nje izvedene metode. Za istu namjenu mogu se rabiti različite inačice evociranih potencijala (EP), senzornih i motornih. Zajedničko obilježje svih ovih tehnika je vizualni prikaz prostorno i vremenski sumirane neuronske aktivnosti, što je omogućeno specifičnom strukturnom i funkcijskom organizacijom mozga. Glede podrijetla EEG aktivnosti, velike populacije usporedno orijentiranih neurona omogućavaju stvaranje prolaznih električnih gradijenata napona kojih su dostatni da bi se zabilježili na površini vlasišta. U usporedbi s metodama neuroprikazivanja, glavna prednost neurofizioloških metoda je njihova visoka vremenska rezolucija kakvu nije moguće postići niti posljednjim generacijama funkcijskog prikazivanja magnetskom rezonancom (fMRI), kao i brzina kojom se elektrofiziološki parametri pojavljuju tijekom patofizioloških procesa u mozgu. Međutim, zajedničko obilježje zabilježenih neurofizioloških parametara je to što su oni rezultat složene mozgovne integracije prostorno udaljenih neuralnih mreža. To pak za sobom povlači znatno slabiju prostornu rezoluciju u usporedbi sa standardnim tehnikama slikovnog prikazivanja.

U rutinskoj dijagnostici moždanog udara koji se može definirati kao iznenadna pojava neurološkog deficita koji se može pripisati žarišnoj vaskularnoj patologiji[1], neurofiziološke metode u većini slučajeva nisu indicirane. One ne mogu zamijeniti suvremene tehnike slikovnog prikazivanja niti po vrijednosti u lokalizaciji niti specifičnošću nalaza. Uz to, ne može se donijeti nikakav izravan zaključak u svezi s vaskularnom patologijom. Ipak, postoje situacije u dijagnostici moždanog udara kad neurofiziološke metode imaju prednost pred onima neuroprikazivanja. Primjerice, takva je situacija kad ishemijsko oštećenje još nije postalo vidljivo na prikazima kompjutorizirane tomografije (CT). Za razliku od CT, EEG će nenormalnosti prikazati gotovo istodobno s poremećajem krvnog protoka. Obično se može razlikovati supratentorijalno od infratentorijalnog oštećenja ili od manjih hemisfernih oštećenja u subkortikalnim

blood flow failure. It is commonly possible to differentiate cortical supratentorial from infratentorial lesion, or from minor hemispheric lesions in the subcortical structures. Cortical lesions are characterized by the slow activity with maximal changes in parietotemporal regions. The periodical lateralized epileptiform discharges (PLEDs) can be seen less frequently. This pattern is not nosologically specific, but in the context of stroke diagnosis the possibility of the watershed infarction that has some diagnostic and therapeutic implications should be kept in mind. In minor subcortical hemispheric lesions, except those affecting mesencephalic tegmentum and thalamic structures, EEG is normal or shows only slight abnormalities. Also, EEG can be useful in the diagnosis of the infarcts in the inferior part of the brainstem. In some patients with this syndrome EEG pattern is characterized by the normal alpha rhythm that does not show expected desynchronization after sensory stimulation. In some centers EEG recording is part of the operative monitoring during the carotid surgery. During these procedures arterial clamping is promptly followed by EEG changes that can be visually and digitally analyzed, and the information thus obtained can be helpful in further operative decisions, especially regarding shunting.

The application of digital processing of the recorded bioelectrical potentials can significantly increase diagnostic sensitivity of the EEG. In terms of frequency spectra and the potential amplitude, the EEG signal can by analyzed in the chosen sequence of time. The data obtained in this way can be displayed as a quantitative analysis and/or topographic map on the scalp projection. These techniques are sometimes referred to as brain mapping, although some authors think that this term should be used more restrictively, only for topographic displays[2]. By the use of quantitative analysis, it is possible to reveal discrete changes in EEG records that are very difficult to diagnose only by visual analysis. During the acute phase of stroke lateralized abnormalities can be found by visual analysis in 40%-70% of patients[2]. This percentage can be increased to up to 90% by the use of quantitative EEG[3,4]. The localizational value can also be increased, as in terms of projection of pathologic electrogenerator on the scalp surface[5], so in relation to deeper structures[6]. However, even by use of the mentioned technical progress, it has not been possible to increase the nosologic specificity that is necessary to differentiate cerebral infarcts from hemorrhage and other expansive processes.

Quantitative analysis confirmed the high sensitivity of EEG for changes of the cerebral blood flow. The EEG

strukturama. Kortikalne lezije su obilježene polaganom aktivnošću s maksimalnim promjenama u parietotemporalnim područjima. Rjeđe se mogu vidjeti periodični lateralizirani epileptiformni izboji (PLED). Ovakva situacija nije nozološki specifična, ali u kontekstu moždanog udara valja imati na umu mogućnost infarkt sliva (*watershed infarction*) s dijagnostičkim i terapijskim implikacijama. Kod manjih subkortikalnih hemisfernih oštećenja, osim onih koja zahvaćaju mezencefalni tegment i strukture talamusa, EEG je normalna ili pokazuje samo blaže nenormalnosti. EEG može isto tako biti korisna u dijagnostici infarkta donjeg dijela moždanog debla. U nekih bolesnika s ovim sindromom EEG zapis je obilježen normalnim alfa ritmom koji ne pokazuje očekivanu desinkronizaciju nakon osjetilne stimulacije. U nekim centrima je zapis EEG dio operacijskog praćenja tijekom zahvata na karotidama. Tijekom ovih zahvata promjene u EEG slijede odmah nakon postavljanja stezaljka na karotidu i mogu se vizualno i digitalno analizirati, a tako dobiveni podaci mogu pomoći u daljnjim operacijskim odlukama, poglavito glede postavljanja međuspoja (*shunting*).

Digitalnom obradom zabilježenih bioelektričnih potencijala može se značajno povećati dijagnostička osjetljivost EEG. Što se tiče frekvencijskih spektara i amplitude potencijala, EEG signal se može analizirati u odabranom vremenskom slijedu. Tako dobiveni podaci mogu se prikazati kao kvantitativna analiza i/ili topografska karta na projekciji vlasišta. Ove tehnike ponekad se nazivaju "mapiranjem" mozga, iako neki autori smatraju kako ovaj izraz treba strože primjenjivati i to samo za topografske prikaze[2]. Uz primjenu kvantitativne analize mogu se otkriti fine promjene u EEG zapisima koje je teško dijagnosticirati samo vizualnom analizom. Za vrijeme akutne faze moždanog udara lateralizirane nenormalnosti mogu se naći vizualnom analizom u 40%-70% bolesnika[2]. Ovaj se postotak može povisiti do 90% primjenom kvantitativne EEG[3,4]. Može se povećati i lokalizacijska vrijednost, kako u smislu projekcije patološkog elektrogeneratora na površini vlasišta[5], tako i glede dubljih struktura[6]. Međutim, čak ni uporabom spomenutog tehničkog napretka nije se mogla povećati nozološka specifičnost koja je potrebna za razlikovanje moždanih infarkta od krvarenja i drugih ekspanzivnih procesa.

Kvantitativna analiza je potvrdila visoku osjetljivost EEG za promjene moždanog krvotoka. Spektri EEG, poglavito oni delta-frekvencije, pokazali su visoke koeficijente korelacije (oko 90%) s regionalnim krvotokom i metabolizmom kisika mjerenim tomografijom s emitiranjem pozitrona (PET)[7]. Klinička primjena analize frekvencija ponovno je potvrdila potencijal EEG da bilježi promjene

spectra, especially those of delta-frequency, showed high correlation coefficients (~90%) with regional blood flow and oxygen metabolism measured by positron emission tomography (PET)[7]. Clinical applications of frequency analysis reaffirmed the EEG potential to be able to record changes of bioelectrical potentials caused by cerebral hypoperfusion even before they could be demonstrated by CT. Besides, by use of these methods it was demonstrated that it could be sometimes possible to reveal the abnormalities that could not, even later on, be shown by brain CT, which is the case in some transient and reversible ischemic episodes[8]. Based on these and similar studies, it can be concluded that EEG is a sensitive and adequate method in the detection of cerebral dysfunction caused by hypoperfusion and hypometabolism. The spectral analysis of EEG records increased the sensitivity and reliability of monitoring during carotid endarterectomies[9,10]. Despite these advantages, EEG is relatively rarely used in standard stroke diagnosis. The main reason is that, after a complete neurologic examination supplemented by neuroimaging and neurosonologic investigations, there are only a few relevant clinical questions left. There is no doubt that quantitative EEG and related techniques have a great value in the scientific studies, but its clinical use is to some extent limited by the problems related to the correct interpretation of finding that is not rarely further aggravated by several exogenous and endogenous artefacts.

The clinical usefulness of the remaining neurophysiologic techniques in the stroke diagnosis has similar limitations as EEG. For instance, the findings of sensory evoked potentials in the clinical context of the acute stroke diagnosis do not show a specificity of changes that is evident in some other diseases. Moreover, the localizational value of evoked potentials is far behind the neuroimaging findings. However, there are clinical questions that cannot be answered even by modern MR studies, but by use of additional electrophysiologic examinations useful information can still be obtained. An example is the pontine infarct that can be followed by the cochlear infarct, too. Affection or nonaffection of cochlea in this clinical picture can be detected by brainstem auditory evoked potentials (BAEP)[11]. The neurophysiologic techniques can also be used in localization of other brainstem syndromes, especially if MRI is not available. The example for such applications of BAEP is a locked-in syndrome[12]. Similarly, localization of the infarct in Wallenberg's syndrome can by facilitated by the analysis of blink-reflex[13]. Visual and somatosensory evoked potentials can also be used in objectifying the lesions caused by stroke, but in the routine diagnosis they are commonly not indicated.

bioelektričnih potencijala uzrokovane moždanom hipoperfuzijom čak i prije nego što se oni mogu dokazati na CT. Uz to, uporabom ovih metoda dokazano je kako se ponekad mogu otkriti nenormalnosti koje se ne mogu, čak ni kasnije, prikazati pomoću CT mozga, što je slučaj u nekim prolaznim i reverzibilnim ishemijskim ispadima[8]. Na osnovi ovih i sličnih ispitivanja može se zaključiti kako je EEG osjetljiva i odgovarajuća metoda u otkrivanju moždane disfunkcije uzrokovane hipoperfuzijom i hipometabolizmom. Spektralna analiza EEG zapisa povećala je osjetljivost i pouzdanost praćenja tijekom karotidnih endarterektomija[9,10]. Usprkos ovim prednostima EEG se relativno rijetko rabi u standardnoj dijagnostici moždanog udara. Glavni razlog tome je to što nakon potpunog neurološkog pregleda dopunjenog pregledima pomoću neuroprikazivanja i neurosonologije preostaje malo važnijih kliničkih pitanja. Nema sumnje da kvantitativna EEG i s njom povezane tehnike imaju veliku vrijednost u znanstvenim istraživanjima, no njihova klinička primjena je donekle ograničena problemima povezanim s ispravnim tumačenjem nalaza koji se nerijetko i dalje pogoršava nekolicinom egzogenih i endogenih artefakata.

Klinička korisnost preostalih neurofizioloških tehnika u dijagnostici moždanog udara ima slična ograničenja kao EEG. Na primjer, nalazi senzornih evociranih potencijala u kliničkom kontekstu dijagnostike akutnog moždanog udara ne pokazuju specifičnost promjena koja je očita kod nekih drugih bolesti. Štoviše, lokalizacijska vrijednost evociranih potencijala daleko zaostaje za onom kod nalaza neuroprikazivanja. Međutim, postoje klinička pitanja na koja ne mogu odgovoriti niti ispitivanja suvremenom MR, dok se primjenom dodatnih elektrofizioloških pregleda ipak mogu dobiti korisni podaci. Primjer za to je pontinski infarkt nakon kojega može uslijediti i kohlearni infarkt. Zahvaćenost ili nezahvaćenost kohleje kod ovakve kliničke slike može se otkriti pomoću slušnih evociranih potencijala moždanog debla (BAEP)[11]. Neurofiziološke tehnike mogu se isto tako rabiti u lokaliziranju drugih sindroma moždanog debla, osobito ako MRI nije dostupno. Primjer za takvu primjenu BAEP je sindrom "zabravljenosti" (*locked-in syndrome*)[12]. Slično tome, lokalizaciju infarkta kod Wallenbergova sindroma olakšati će analiza refleksa žmirkanja[13]. Vidni i somatosenzorni evocirani potencijali mogu se isto tako primijeniti u objektiviranju oštećenja uzrokovanih moždanim udarom, no u rutinskoj dijagnostici oni obično nisu indicirani.

Kako je gore naglašeno, neurofiziološke metode danas kod većine bolesnika imaju dopunsku ulogu u standardnoj dijagnostici moždanog udara[14]. Međutim, ako se pojam

As emphasized above, neurophysiologic methods have nowadays a supplemental role in the standard stroke diagnosis for the majority of patients[14]. However, if the term stroke diagnosis is considered more widely and if it includes the process of diagnosing clinical consequences of the initial accident, and also the follow-up of the neurologic impairment, the neurophysiologic methods will be in quite different position. In that case they are complementary or leading in comparison to neuroimaging and neuropsychologic methods. In this context, it can be expected from the neurophysiologic methods to bring information with a primarily functional value. So, the quantitative EEG proved to be a valuable tool for monitoring effects of antiedemic therapy in patients with stroke[15,16], and in some prognostic evaluations[17,18]. Among evoked potentials, the priority could be given to the endogenous evoked potentials. The endogenous EPs are less dependent on the characteristics of peripheral stimulations. They are in principle an expression of cortical and/or subcortical processing. The synonymously used term is the Event Related Potentials (ERP), and the best known technique is P 300 or P3 wave. This method may also be referred to as "cognitive potential" because it is a potential that is evoked by active processing of the perceived stimulus in the state of complete alertness. The ERP methods are aimed to define the neurophysiologic correlates of some language functions[19,20], and some studies of the applicability in neurorehabilitation after stroke are conducted[21,22].

All of these methods are still developing, and their role in stroke diagnosis and in the follow-up of its consequences must yet be defined by well designed clinical studies.

The transcranial magnetic stimulation (TMS) is probably the most valuable technique among the motor evoked potentials. By this method it is possible to detect cerebral regions that are engaged in the performing of various motor patterns. It is particularly helpful in studies investigating cerebral plasticity that implies processes of cerebral reorganization. Using TMS, it is possible to block certain transitory neural networks, which can also lead to detection of cortical structures participating in the activities that are of interest. According to its capacities TMS might be an important tool in diagnosing functional and structural changes that occur during the stroke rehabilitation[22,23].

dijagnostike moždanog udara razmatra u širem smislu i ako ona uključuje proces dijagnosticiranja kliničkih posljedica početnog događaja, kao i praćenje neurološkog poremećaja, tada su neurofiziološke metode u sasvim drukčijem položaju. U tom slučaju one su komplementarne ili vodeće u usporedbi s metodama neuroprikazivanja i neuropsihološkim metodama. U tom kontekstu se od neurofizioloških metoda može očekivati da će pružiti podatke koji su prvenstveno od funkcijske važnosti. Tako se je kvantitativna EEG pokazala korisnom u praćenju učinaka protuedemske terapije u bolesnika s moždanim udarom[15,16], te kod nekih prognostičkih procjena[17,18]. Među evociranim potencijalima prednost bi se mogla dati endogenim evociranim potencijalima. Endogeni EP su manje ovisni o značajkama perifernih podražaja. Oni su u načelu izraz kortikalne i/ili subkortikalne obrade. Kao sinonim se rabi izraz "potencijali povezani s događajem" (*event related potentials,* ERP), a najpoznatija tehnika je val P300 ili P3. Ovu metodu može se nazvati i "spoznajnim potencijalom", jer je moguće da se evocira aktivnom obradom zapaženog podražaja u stanju potpune budnosti. Cilj metoda ERP je definirati neurofiziološke korelate nekih jezičnih funkcija[19,20], a provedene su i neke studije njihove primjenjivosti u neurorehabilitaciji[21,22]. Sve ove metode se još razvijaju i njihovu ulogu u dijagnostici moždanog udara i praćenju njegovih posljedica treba tek utvrditi u dobro zamišljenim kliničkim ispitivanjima.

Transkranijska magnetna stimulacija (TMS) vjerojatno je najvrijednija tehnika među motornim evociranim potencijalima. Ovom metodom se mogu otkriti moždane regije koje su uključene u izvođenje raznih motornih aktivnosti. Ona je osobito korisna u ispitivanju plastičnosti mozga koja uključuje procese moždane reorganizacije. Uz primjenu TMS mogu se blokirati određene tranzitorne neuralne mreže, što može također dovesti i do otkrivanja kortikalnih struktura koje sudjeluju u aktivnostima koje nas zanimaju. Zahvaljujući njenim mogućnostima TMS bi mogla biti važno sredstvo u dijagnosticiranju funkcijskih i strukturnih promjena koje se događaju za vrijeme rehabilitacije od moždanog udara[22,23].

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NEUROIMAGING METHODS IN THE DIAGNOSIS OF STROKE
METODE SLIKOVNOG PRIKAZA U DIJAGNOSTICI MOŽDANOG UDARA

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In the diagnosis of stroke, computed tomography (CT) has an advantage over other neuroimaging techniques. CT is based on the measurement of tissue structural density expressed in Hounsfield units (HU). Over the last few years, sophisticated advancements have been achieved in CT, so that spiral CT devices with continuously rotating x-ray tube with simultaneous continuous movement of x-ray table, thus reducing the examination to only a few minutes. The use of ever better detectors has also entailed improved image resolution. Technologic advances have enabled CT imaging of blood vessels (CT angiography), thus greatly reducing the use of invasive methods such as digital subtraction angiography (DSA).

Magnetic resonance (MR) operates on the principle of recording H ions in the electromagnetic field. As differentiated from CT, MR allows for a multiplanar image in three projections and because of higher resolution enables better visualization of anatomic intracranial structures and earlier diagnosis of many intracranial pathologic changes. With the use of sophisticated computer elements, improved software and hardware, magnetic field enhancement, and specific imaging sequences MR is currently an ideal, noninvasive method for the diagnosis of various types of stroke. Also, MR enables visualization of intracranial and extracranial arteries (MRA) as well as of the venous system with venous sinuses (MRV). Thus, MR has reduced indications for DSA on screening for intracranial vascular disease of the brain, offering an opportunity for noninvasive multiplanar study of cerebral blood vessels. A disadvantage of the method is inadequate visualization of small, distal vascular branches, inadequate information on flow direction, dependence on blood flow and on patient's compliance, as the patient must stay still during the imaging process. As stroke patients are quite restless in the acute stage of the disease, CT is preferred in this stage.

MR and MRA are recommended for evaluation of intracranial vascular pathology, e.g., stroke, arterial stenosis and obliteration, aneurysm, arteriovenous malformations, then on diagnosis of various entities of vascular pathology, especially venous diseases, vague clinical cases, on differential diagnosis, etc.

Kompjutorizirana tomografija (CT) ima prednost pred drugim tehnikama neuroprikazivanja u dijagnostici moždanog udara. Metoda se zasniva na mjerenju gustoće strukture tkiva izražene u Hounsfieldovim jedinicama (HU), a posljednjih je godina usavršena te su u upotrebi spiralni CT uređaji s kontinuiranom rotacijom rentgenske cijevi uz istodobno neprekidno pomicanje rentgenskog stola. Na taj način se ubrzava pretraga na samo nekoliko minuta. Uporabom sve boljih detektora poboljšava se i rezolucija slike. Napredak u tehnologiji omogućio je i prikaz krvnih žila pomoću CT (CT angiografija), te se uvelike smanjuje uporaba invazivnih metoda kao što je digitalna subtrakcijska angiografija (DSA).

Magnetska rezonanca (MR) radi na načelu egistriranja H iona u elektromagnetskom polju. Za razliku od CT ona omogućuje multiplanarni prikaz u tri ravnine, a s obzirom na postizanje bolje rezolucije omogućuje bolji prikaz anatomskih intrakranijskih struktura, te raniju dijagnostiku mnogih intrakranijskih patoloških promjena. Primjenom sofisticiranih kompjutorskih elemenata, poboljašnjem programa i samih uređaja, pojačanjem magnetskog polja i upotrebom specifičnih sekvenca snimanja MR zasad čini idealnu neinvazivnu metodu u dijagnostici različitih oblika moždanog udara. MR omogućuje i prikaz intrakranijskih te ekstrakranijskih arterija (MRA), ali i prikaz venskog sustava s venskim sinusima (MRV). Tako MRA i MRV smanjuju indikacije za DSA u probiru intrakranijskih vaskularnih bolesti mozga zbog mogućnosti neinvazivnog multiplanarnog pregleda krvnih žila mozga. Nedostatak ove metode je nedostatan prikaz malih distalnih ogranaka krvnih žila, nedostatni podaci o smjeru protoka, ovisnost o protoku krvi te o bolesnikovoj suradnji – bolesnik mora biti miran za vrijeme snimanja, a s obzirom na to da su bolesnici s cerebrovaskularnim inzultom u akutnoj fazi nemirni, u toj fazi prednost ima CT.

MR i MRA se preporučuju u procjeni intrakranijske vaskularne patologije: cerebrovaskularnog inzulta, arterijskih stenoza i obliteracija, aneurizma, arterijsko-venskih malformacija, u dijagnostici različitih entiteta vaskularne patologije, naročito u dijagnostici venskih bolesti, u nejas-

Stroke

Stroke is an acute or subacute occurrence of symptoms caused by localized impairment of cerebral arterial circulation. Stroke morbidity and mortality rise with age, especially after the age of 50. The risk factors for stroke include arterial hypertension, cardiac diseases (especially arrhythmias), hypercholesterolemia, diabetes mellitus, etc.

Ischemic infarction or infarction due to decreased cerebrovascular flow caused by thrombotic or embolic occlusion of cerebral arteries underlie 85% of stroke cases, whereas hemorrhagic infarction is found in the rest of 15%. Ischemic infarction is visualized on CT as a hypodense zone, which reflects a necrotic process and follows its own course of development. The image density varies as the necrotic process passes through various stages. These alterations can be followed by CT and especially by MR.

Two areas are differentiated in every focal ischemia of the brain, i.e. central ischemic area and peripheral area of so-called ischemic penumbra. The central area is an area of total ischemia where complete interruption of the blood supply has occurred, i.e. center of the lesion. The metabolic and morphological alterations occurring in this area are progressive and irreversible. In the peripheral area, however, some circulation has yet been preserved but is characterized by hypoperfusion. Either reparable or irreparable lesions may develop in this area, depending on further course of the process. In case of reparable lesions, the clinical picture will improve and a regression pattern is seen on CT or MR in the marginal region in the subacute stage of the disease. In case of irreparable lesions, in contrast, the process in the central and peripheral areas is unified and they cannot be differentiated anymore.

Cerebral edema has a very important role in the evaluation of ischemic lesion and its outcome. Cerebral edema develops consequentially to ischemia, and also stimulates further expansion of ischemic lesion due to its mechanical action. Colliquative necrosis will demarcate the process, so that the infarcted area becomes wedge shaped. Prolonged duration of colliquative necrosis leads to the occurrence of cysic/pseudocystic formations that are clearly visualized on CT and MR.

CT finding in the acute stage of stroke is characterized by homogeneous, subtle hypodensity resembling mist. In this stage, the lesion appears oval, unsharply delineated from the surrounding intact tissue. In the peripheral ischemic area, CT shows slight hyperdense shadow that corresponds to an attempt at forming collateral circulation and blood-brain barrier failure.

nim kliničkim slučajevima, u diferencijalnoj dijagnostici i sl.

Moždani udar je akutni ili subakutni nastanak simptoma uzrokovanih lokaliziranim poremećajem arterijske cirkulacije mozga. Pobol i smrtnost rastu s porastom životne dobi, osobito iznad 50. godine. Rizični čimbenici za razvoj moždanog udara su arterijska hipertenzija, srčane bolesti (osobito aritmije), hiperkolesterolemija, šećerna bolest i sl.

U 85% slučajeva cerebrovaskularnog inzulta nalazi se ishemijski infarkt ili onaj nastao smanjenjem moždanog protoka zbog trombotične ili embolijske okluzije moždanih arterija, a u 15% hemoragijski infarkt.

Ishemijski infarkt prikazuje se na CT kao zona snižene gustoće (hipodenzna zona) koja je odraz nekrotičnog procesa koji pak ima svoj tijek razvoja. Kako nekrotični proces prolazi kroz različite faze, tako se mijenja i gustoća slike. Te se promjene mogu pratiti pomoću CT, a osobito pomoću MR.

Kod svake žarišne ishemije u mozgu razlikuju se dvije zone: središnja zona ishemije i periferna zona, tj. "zona penumbre". Središnja zona je područje potpune ishemije u kojem je došlo do potpunog prekida dotoka krvi, odnosno središte lezije. Metaboličnе i morfološke promjene koje nastaju u ovoj zoni progresivno se razvijaju i ireverzibilne su. U perifernoj zoni, međutim, još uvijek postoji cirkulacija, ali hipoperfuzijske naravi. Ovisno o daljnjem razvoju procesa u ovom području mogu se razviti popravljive ili nepopravljive promjene. U slučaju popravljivih promjena dolazi do poboljšanja u kliničkoj slici, a na nalazima CT i MR vide se regresivne promjene u rubnom području u subakutnoj fazi. Kod nepopravljivih promjena, međutim, dolazi do izjednačavanja procesa u središnjem i rubnom području koja se više ne mogu razlikovati.

Vrlo važnu ulogu u procjeni ishemijske lezije i njezinog ishoda ima cerebralni edem. Cerebralni edem se razvija kao posljedica ishemije, ali isto tako potiče daljnje povećanje ishemijske lezije zbog svog mehaničkog djelovanja. Kolikvacijska nekroza tijekom procesa demarkira proces pa infarktom zahvaćeno područje poprima oblik klina. Dulje trajanje kolikvacijske nekroze uzrokuje stvaranje cističnih/pseudocističnih formacija jasno prikazanih na CT i MR.

Nalaz CT u akutnoj fazi je obilježen hipodenzitetom homogenije, nježnije naravi, nalik na maglu. Oblik promjene je u ovoj fazi ovalan, neoštro ograničen od okolnog zdravog tkiva. U perifernom području ishemije CT pokazuje blagu hiperdenznu sjenu koja odgovara pokušaju stvarnja kolateralne cirkulacije i popuštanju hematoencefalne barijere.

CT nam omogućuje preciznu lokalizaciju ne samo promjena na samom mozgu, nego i posredno otkrivanje

CT allows for precise localization of not only brain lesions but indirectly also detection of the occluded vessel. Detection of lesions depends on the size and age, localization, shape and relation of the brain lesion to the surrounding structures. The regions rather difficult for CT analysis because of numerous artifacts from the adjacent osseous structures are medulla oblongata, pons and hippocampal structures. However, with the introduction of spiral CT for diagnostic purpose, some problems such as restless patients with difficult breathing, seriously ill patients, comatose patients, etc., have been eliminated.

Ischemic Infarction

Ischemic disease of the brain is a necrotic or necrotizing process that develops due to the loss or reduction of blood flow through cerebral circulation, evolving through a number of morphological stages, from initial edema and tissue disintegration through demarcation, incapsulation and possible cicatricial reparation. Ischemic infarcts are largely involved by colliquative necrosis that ultimately leads to encephalomalacia. The evolution of ischemic infarction can be followed on CT, by measuring the density of absorption coefficients of the affected region. A hypodense zone in the particular vessel irrigation area points to a recent onset of ischemia (within few hours); its quantitative value varies during the course of the disease and shows progressive decrease to form a cystic structure containing CSF resembling fluid after three weeks.

The superacute stage (up to 24 h) is characterized by hypodensity of the infarcted area due to water absorption to the necrotic tissue and formation of a cytotoxic edema of not only neurons but also of other infarcted cells. CT shows an extensive hypodense area in the supply region of the occluded artery as well as hemorrhages.

In the acute stage (24 h – day 7) a vasogenous edema becomes apparent due to the blood-brain barrier failure consequential to extravasal edema, especially in the white matter. CT shows progressive density decrease and ever clearer demarcation of the involved area. The mass effect increases over the first 3 days and CT shows a wedge shaped, hypodense area involving both white and gray matter.

In the subacute stage (day 8-21), especially in case of embolic incidents, hemorrhage (transformation) to the infarcted area may occur. The blood is shed to the peripheral parts of the involved area secondary to the abrupt onset of blood vessel occlusion along with undeveloped collateral flow, which results in rupture of small blood vessels and hemorrhages due to high pressure and large amount

okludirane krvne žile. Otkrivanje lezija ovisi o veličini i starosti lezije, lokalizaciji, obliku i odnosu promjene u mozgu prema okolnim strukturama. Problematična područja za analizu pomoću CT, gdje se pojavljuje čitav niz artefakata zbog okolnih koštanih struktura, su medula oblongata, pons i hipokampusne strukture. Međutim, uvođenjem u dijagnostiku spiralnog CT uklonjeni su neki od problema, kao što su nemirni bolesnik s otežanim disanjem, teški bolesnici, npr. oni u komi i sl.

Ishemijski infarkt

Ishemijska bolest mozga je nekrotični ili nekrotizirajući proces nastao gubitkom ili smanjenjem protoka kroz moždanu cirkulaciju, koji prolazi kroz čitav niz morfoloških stadija razvoja: od početnog edema i dezintegracije tkiva do demarkacije, inkapsulacije i mogućeg ožiljkastog popravljanja. Velik dio ishemijskih infarkata zauzima kolikvacijska nekroza koja kao krajnji rezultat ima encefalomalaciju. Evolucija ishemijskog infarkta može se pratiti pomoću CT mjerenjem gustoće koeficijenata apsorpcije oštećenog područja. Područje snižene gustoće (hipodenzitet) u irigacijskom području određene krvne žile ukazuje na nedavni nastup ishemije (traje unatrag nekoliko sati). Njegova se kvantitativna vrijednost mijenja tijekom bolesti, tako da se progresivno snizuje te nakon tri tjedna dolazi do stvaranja cistične strukture koja sadrži tekućinu gustoće likvora.

U superakutnoj fazi (do 24 h) dolazi do hipodenziteta infarciranog područja zbog uvlačenja vode u nekrotično tkivo i nastanka citotoksičnog edema ne samo neurona, nego i ostalih infarciranih stanica. CT pokazuje ekstenzivno područje niske gustoće u opskrbnom području začepljene arterije, kao i zone krvarenja.

U akutnoj fazi (24 h do 7. dan) postaje očit vazogeni edem zbog kraha krvnomoždane barijere kao posljedica ekstravazalnog edema, osobito u bijeloj tvari. CT pokazuje progresivno smanjenje gustoće i sve jasniju demarkaciju zahvaćenog područja. Učinak mase se povećava tijekom prva 3 dana i CT pokazuje klinasto oblikovano područje niske gustoće koje obuhvaća i sivu i bijelu tvar.

U subakutnoj fazi (8.-21. dan), osobito kod embolijskih incidenata, može se pojaviti krvarenje (transformacije) u infarcirano područje. Zbog naglog nastupa okluzije krvne žile i nerazvijenog kolateralnog krvotoka krv naglo navre u periferne dijelove zahvaćenog područja, te zbog visokog tlaka i velike količine dolazi do pucanja sitnih krvnih žila i krvarenja. U slučajevima pomicanja tromba distalno od mjesta gdje je nastupilo začepljenje krvne žile dolazi do ekstravazacije kroz oštećeni dio sada oslobođene krvne žile

of blood. In case of thrombus migration distally from the site of blood vessel occlusion, extravasation through the damaged segment of the now released blood vessel occurs, again with hemorrhage to the infarcted area. These factors are responsible for the variegated picture of ischemic infarction at this stage of the disease, which may mimic tumorous process in some cases. CT image with a contrast showing pathologic, 'luxury' perfusion of cortical areas of the cerebral artery supply is used for further evaluation.

In this period, an expansive pattern may be observed in the infarcted area due to the development of considerable edema, thus the course and prognosis of the disease depend just on the intensity of this event as well as on the possible transtentorial herniation.

In the chronic state (from day 21 on), partial sharp demarcation or cicatrization of the process occur, and CT density will change according to these alterations.

In most cases, native CT proves adequate to make the diagnosis of stroke, especially in the acute and superacute stage when complications may occur. However, in case of uncertain diagnosis or unusual localization of lesions, a MR scan should be obtained.

Contrast medium should not be used in the acute stage; in the subacute stage, complete imbibition or gyral imbibition may be observed (the finding is not pathognomonic and causes difficulties on differential diagnosis from other vascular diseases).

Hemorrhagic Infarction

The incidence of hemorrhagic infarctions in all strokes ranges from 5% to 21%. Hemorrhagic infarction occurs due to secondary hemorrhage into the ischemically altered cerebral region, mostly due to embolism. The hemorrhage occurs during ischemia or consequentially to infarction within 24 h, however, hemorrhagic transformation is only visible 24 h from the onset of hemorrhage.

Hemorrhagic infarction is easily differentiated from cerebral hemorrhage of some other etiology by clinical picture and CT finding. In case of hemorrhagic infarction, the clinical picture develops immediately in full intensity, without signs of intracranial pressure elevation, as differentiated from cerebral hemorrhage which shows signs of intracranial pressure increase along with an abrupt development of clinical picture. Hemorrhagic infarction is most common in embolism and large infarcts.

The hemorrhagic infarction density on CT image is determined by blood density and is between 40 and 80 HU. It is characterized by unsharply delineated margins demarcated by a hypodense area corresponding to the

i ponovno do krvarenja u infarcirano područje. Navedeni čimbenici odgovorni su za to što je slika ishemijskog infarkta u ovoj fazi bolesti šarolika te u pojedinim slučajevima sliči tumorskom procesu. Za daljnju procjenu rabi se CT prikaz s kontrastom koji pokazuje patološko nakupljanje ("*luxury perfusion*") kortikalnih zona područja opskrbe moždane arterije.

U ovom razdoblju zbog razvoja jakog edema može doći do ekspanzivnog ponašanja infarciranog područja, tako da tijek i prognoza bolesti ovise upravo o intenzitetu ovog događaja te o mogućoj transtentorijalnoj hernijaciji.

U kroničnoj fazi (nakon 21. dana) dolazi do djelomičnog oštrog demarkiranja ili ožiljavanja procesa, te će ovisno o promjeni biti i različita gustoća na CT.

U većini slučajeva nativni CT je dovoljan za postavljanje dijagnoze moždanog udara, osobito u akutnoj i superakutnoj fazi kada su moguće i komplikacije. Međutim, u slučajevima nesigurne dijagnoze ili neuobičajene lokalizacije promjena potrebno je učiniti pretragu na uređaju MR.

Kontrastno sredstvo se ne primjenuje u akutnoj fazi, a u subakutnoj fazi oblik imbibicije može biti potpun ili pak može pokazati imbibiciju u obliku giralnog crteža (nalaz nije patognomoničan i stvara poteškoće u diferencijalnoj dijagnozi u odnosu na druge krvnožilne bolesti).

Hemoragijski infarkt

Incidencija hemoragijskih infarkata unutar svih moždanih udara je 5%-21%. Nastaje kao posljedica sekundarnog krvarenja u ishemijski promijenjeno područje mozga koje je najčešće nastalo embolijom. Krvarenje nastaje za vrijeme ishemije ili kao posljedica infarkta unutar 24 h, međutim, hemoragijska transformacija je vidljiva tek 24 h nakon nastupa krvarenja.

Prema kliničkoj slici i nalazu CT lako se razlikuje od moždanog krvarenja druge etiologije. Hemoragijski infarkt razvija kliničku sliku odmah u punom intenzitetu bez znakova povećanja intrakranijskog tlaka, za razliku od moždanog krvarenja koje uz nagli razvoj kliničke slike pokazuje i znakove povišenja intrakranijskog tlaka. Hemoragijski infarkt je najčeći kod embolije i velikih infarkata.

Gustoća hemoragijskog infarkta na CT slici je određena gustoćom krvi i iznosi 40 do 80 HU; obilježen je neoštrim rubom, omeđen zonom snižene gustoće koja odgovara ishemijskom dijelu infarkta ili edemu. Daljnji izgled infarkta ovisi o ponašanju krvnih komponenata u ishemijom zahvaćenom području. S vremenom se gustoća tako mijenja da nakon nekoliko tjedana postaje izodenzna u odnosu na okolne strukture.

U 25% slučajeva CT nalaz može biti potpuno normalan kod jasnih kliničkih slučajeva cerebrovaskularnog inzul-

ischemic part of infarction or edema. Further infarct appearance depends on the behavior of blood components in the ischemic area. Density changes with time and the area becomes isodense with the adjacent structures within a few weeks.

CT finding can be completely normal in 25% of clear cases of stroke. In these cases, MR scanning should be performed. Some 80% of acute infarctions can be detected by MR in the initial stage within 24 h. The earliest change detectable on MR occurs at 2 h of the onset of infarction, is characterized by the sign of intravascular MR signal enhancement, and is caused by slow and decreased intracranial blood flow through the vessel. Cortical edema (hyperintensity, increased thickness and vague border between the cortex and the white matter) is earliest detectable at 3 h of the infarction onset, especially on specific images such as DWI sequence.

MR has multiple role in the diagnosis of stroke; the fast spin echo image shows the extent of ischemic lesion, whereas MRA shows extensive changes in the cerebrovascular system. The diffusion weight image (DWI) based on the change in the content of water in the intracellular and extracellular area is used for early ischemia visualization. As cytotoxic edema is one of the first characteristics of ischemia, these lesions can be very early detected by MR. Thus, MR enables easy differentiation between previous vascular lesions and recent changes. MR has an important role in the detection of ischemic lesions immediately upon the onset of stroke and leads to the cause of stroke.

MRA is used to visualize occluded vessels of the brain, mostly internal carotid artery, antrior cerebral artery, middle cerebral artery, and vertebral artery.

Venous Infarction

Venous infarction (ischemic or hemorrhagic) occurs due to thrombophlebitis or thrombosis of dural arteriovenous fistulas, thus localization of the process depending on the cause (cortical structures or structures along the intracranial sinuses). Morphologically, the infarct resembles arterial infarct. MR is the method of choice.

Specific forms of infarction: borderline infarcts are ischemic lesions at the border of irrigation systems of large cerebral arteries. They account for 10% of cerebral infarcts, and usually are ischemic, less frequently hemorrhagic or mixed. They are well visualized by CT and MR.

Lacunae are small cystic cavities that can be ascribed to primary arterial diseases of deep penetrant branches of large cerebral arteries. The predilection sites are lentiform nucleus, thalamus, caudate nucleus, and internal capsule. Lacunae are better visualized by MR.

ta. U tim slučajevima potrebno je učiniti snimanje magnetskom rezonanacom (MR).

MR može otkriti 80% akutnih infarkata u početnoj fazi do 24 h. Najranija promjena vidljiva na MR je 2 h od nastupa infarkta; obilježava ju znak intravaskularnog pojačanja MR signala, a uzrokovana je sporim i smanjenim intrakranijskim protokom krvi kroz krvnu žilu. Kortikalni edem (hiperintenzitet, povećana debljina i nejasna granica korteksa i bijele tvaari) vidljiv je najranije 3 h od nastupa infarkta, osobito na specifičnim snimakama kao što je sekvenca DWI.

Važnost MR u dijagnostici moždanog udara je višestruka: tzv. *fast spin echo* prikaz pokazuje opseg ishemijske promjene, a MRA pokazuje opsežne promjene na krvožilnom sustavu mozga. Za rani prikaz ishemije rabe se tzv. *diffusion weight* prikaz (DWI) koji se temelji na promjeni sastava vode u unutarstaničnom i izvanstaničnom području. S obzirom na to da je citotoksični edem jedan od prvih značajka ishemije, ove promjene se na MR mogu vrlo rano otkriti. Ova značajka MR omogućuje lako razlikovanje starih vaskularnih lezija od novih promjena. MR igra važnu ulogu u otkrivanju ishemijskih promjena neposredno nakon nastupa moždanog udara te nas vodi k uzroku moždanog udara.

MRA se rabi za prikaz okludiranih krvnih žila mozga, najčešće a. carotis interna, a. cerebri anterior, a. cerebri media i a. vertebralis.

Venski infarkt (ishemijski ili hemoragični) nastaje zbog tromboflebitisa ili tromboze duralnih arteriovenskih fistula, pa će lokalizacija procesa ovisiti o uzroku (kortikalne strukture ili pak strukture uz intrakranijske sinuse). Morfološki izgled infarkta sličan arterijskom. MR je metoda izbora.

Posebni oblici infarkta: granični infarkti su ishemijske lezije na granici irigacijskih sustava većih moždanih arterija. Čine 10% moždanih infarkta, a obično su ishemijski, rjeđe hemoragični ili miješani. Dobro se vizualiziraju pomoću CT odnosno MR.

Lakune su male cistične šupljine koje se mogu pripisati primarnim arterijskim bolestima dubokih penetrantnih ogranaka velikih cerebralnih arterija. Predilekcijska područja su n. lentiformis, talamus, n.caudatus, capsula interna. Bolje se vizualiziraju pomoću MR.

Multiinfarktne lezije istodobno se javljaju u oko 4% slučajeva, dok se u oko 30% slučajeva nalaze višestruke infarktne lezije različitih irigacijskih područja koje su različite starosti. Ovakove lezije se u oko 20% slučajeva nalaze kod dementnih osoba s progresivnom kliničkom slikom i visokom smrtnošću.

Razni klinički entiteti mogu uzrokovati sliku cerebrovaskularnog inzulta:

Multiinfarct lesions occur simultaneously in some 4% of cases, whereas multiple infarct lesions of various irrigation systems and different age occur in in 30% of cases. In 20% of cases, these lesions are found in demented persons with a progressive clinical picture and high mortality.

Various clinical entities may cause the picture of stroke, e.g.:

Hypertensive encephalopathy is a sequel of significant elevation of blood pressure with fluid and protein escape through blood vessel walls, which causes diffuse or local edema. Hypertensive encephalopathy is a chronic complication of hypertension irrespective of etiology. It is common in renal insufficiency, hemolytic-uremic syndrome, in the stage of toxemia in pregnancy, and in thrombotic thrombocytopenic purpura.

The pathohistologic changes occurring consequentially to longterm blood pressure elevation include fibrinoid necrosis, cerebral arterial thrombosis, microinfarcts and petechial hemorrhages. These changes frequently proceed unnoticed and are found accidentally on CT or MR. Cerebral edema is found in the acute stage and resolves with therapy, whereas in chronic stage lacunar infarcts of CSF density are detected on CT or of CSF signal on MR.

Fibromuscular dysplasia is a rare anomaly with 90% of cases recorded in women aged 40-60. It involves the high segment of internal carotid artery (95%) and/or vertebral artery (25%), with bilateral involvement in 60% of cases. Fibromuscular dysplasia is frequently associated with intracranial aneurysms (20%-50%), arteriovenous fistulas, and renal fibromuscular dysplasia. It frequently assumes a silent course clinically, however, occasionally it may cause focal neurologic deficits with headaches.

Cerebral vasculitis is characterized by inflammation and fibroid necrosis of the arterial media and intima, causing occlusions, infarcts and hemorrhages. The causes may be infective (bacterial, viral, etc.) or noninfective (polyarteritis nodosa, temporal arteritis, granulomatous angiitis, sarcoidosis, etc.).

Spontaneous cerebral hemorrhages occur consequentially to hypertension, atherosclerosis, ruptured aneurysm, A-V malformation, amyloid angiopathy, anticoagulant therapy, tumor hemorrhage, etc. CT is valuable for appropriate and early detection of blood components expressed in HU units. The process density decreases with the duration of hemorrhage from 60 HU down. Men aged 60-80 with a history of hypertension are most commonly affected. The most common localizations are basal ganglia (60%-70%), thalamus (10%-20%), pons (5%), dentate nucleus (1%-5%) and hemispheres (1%-2%).

Hipertenzivna encefalopatija je posljedica značajnog povišenja krvnog tlaka s bijegom tekućine i proteina kroz stijenke krvnih žila, što uzrokuje difuzni ili lokalni edem. Hipertenzivna encefalopatija predstavlja kroničnu komplikaciju hipertenzije bez obzira na etiologiju. Često se javlja kod bubrežne insuficijnecije, hemolitično-uremičnog sindroma, u fazi toksemije u trudnoći, kod trombotične trombocitopenične purpure.

Patohistološke promjene koje nastaju kao posljedica dugotrajno povišenog krvnog tlaka su fibrinoidna nekroza, tromboza moždanih arterija, mikroinfarkti i petehijska krvarenja. Često ove promjene prođu klinički nezapažene pa se nalaze kao slučajan nalaz na CT i MR. U akutnoj fazi nalazi se moždani edem koji se povlači uz terapiju, a u kroničnoj fazi lakunarni infarkti gustoće likvora na CT, odnosno na MR signala likvora.

Fibromuskularna displazija je rijetka anomalija koja u 90% slučajeva zahvaća žene od 40-60 godina starosti. Zahvaća visoko područje unutarnje karotidne arterije (95%) i/ili vertebralne arterije (25%). U 60% slučajeva je bilateralna. Često je udružena s intrakranijskim aneurizmama (20%-50%), arterijskovenskim fistulama i bubrežnom fibromuskularnom displazijom. Često je klinički mukla, no ponekad izaziva žarišne neurološke deficite s glavoboljama.

Cerebralni vaskulitis je obilježen upalom i fibroidnom nekrozom medije i intime arterija uzrokujući okluzije, infarkte ili krvarenja. Uzročnici mogu biti infektivni (bakterijski, virusni i dr.) ili neinfektivni (poliarteritis nodosa, temporalni arteritis, granulomatozni angiitis, sarkoidoze i dr.).

Spontana moždana krvarenja posljedica su hipertonije, ateroskleroze, rupture aneurizme ili A-V malformacije, posljedica amiloidne angiopatije, antikoagulantne terapije, krvarenja u tumoru i sl. Vrijednost CT je u dobrom i ranom otkrivanju krvnih elemenata pomoću HU. S dužinom trajanja krvarenja opada gustoća procesa od 60 HU naniže. Najčešće obolijevaju muškarci od 60-80 godina starosti s anamnezom hipertenzije. Najčešća lokalizacija su bazalni gangliji (60%-70%), talamus (10%-20%), pons (5%), n. dentatus (1%-5%) te hemisfere (1%-2%).

MR omogućuje razlikovanje različitih faza intracerebralnih krvarenja te se na taj način može prilično točno odrediti starost krvarenja. Promjenom MR signala razlikuje se faza oksihemoglobina (unutar 12 sati), deoksihemoglobina (1-7 dana), unutarstaničnog methemoglobina (3-7 dana), izvanstaničnog methemoglobina (poslije 5 dana). Hemosiderin koji nastaje nakon nekoliko tjedana posjeduje paramagnetska svojstva s različitim signalima u različitim tehnikama snimanja.

MR allows for different stage of intracerebral hemorrhage to visualize, thus being able to quite precisely determine the age of hemorrhage. By changing MR signal, the stages of oxyhemoglobin (within 12 h), deoxyhemoglobin (day 1-7), intracellular methemoglobin (day 3-7) and extracellular methemoglobin (day 5 on) can be distinguished. Hemosiderin, formed after a few weeks, possesses paramagnetic properties with different signals on different imaging techniques.

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THE ROLE OF ACUTE STROKE UNIT
ULOGA JEDINICE ZA LIJEČENJE MOŽDANOG UDARA

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Treatment of patients with ischemic stroke at a stroke unit significantly reduces mortality, disability and need of institutional care compared with treatment at general medical wards.

Stroke unit is a hospital unit that exclusively takes care of stroke patients. Stroke units are characterized by specifically trained staff and a multidisciplinary approach to treatment and care. The multidisciplinary core team at stroke unit consists of a neurologist, an internist, nurses and physiotherapists, whereas the extended multidisciplinary team includes speech therapists, occupational therapists and social workers.

There are different types of stroke units: intenisive care units, acute stroke unit, combined acute and rehabilitation stroke unit, and mobile stroke team.

Intensive care units: dedicated stroke units with facilities like ventilators and intensive and nonintensive monitoring. The units are focused on very acute care for a selected group of acute stroke patients and have little focus on rehabilitation.

Liječenje bolesnika s ishemijskim moždanim udarom u jedinicama za liječenje moždanog udara (JLMU) dokazano značajno snižava smrtnost, invaliditet i potrebu za trajnim smještajem u usporedbi s liječenjem bolesnika na općim odjelima. Jedinica za liječenje moždanog udara je bolnički odjel koji se isključivo skrbi o bolesnicima s moždanim udarom, a obilježena je primjereno obrazovanim i multidisciplinskim timom. Multidisciplinski uži tim čine neurolog obrazovan za liječenje bolesnika s moždanim udarom, internist, primjereno obrazovane medicinske sestre i fizioterapeut, a u širem timu su još logoped, radni terapeut i socijalni radnik.

Organizacijski su mogući razni modeli JLMU: intenzivna skrb, jedinica za akutno liječenje moždanog udara, kombinirane akutno-rehabilitacijske jedinice, te mobilni timovi.

Intenzivna skrb: specijalni odjel s opremom (respirator, intenzivno i neinvazivno monitoriranje) za hitno zbrinjavanje bolesnika s teškom kliničkom slikom moždanog udara (komatozni bolesnici, bulbarna paraliza). Slaba ili nikakva rehabilitacija.

Acute stroke units: stroke units that provide acute care for patients but discharge them early (usually within 7 days) and have no or at best a modest focus on rehabilitation. The units do not have intensive care facilities but usually facilities for noninvasive monitoring of vital signs.

Combined acute-rehabilitation stroke units: dedicated stroke units which accept stroke patients for acute treatment combined with early mobilization and rehabilitation for a period of at least 1-2 weeks.

Mobile stroke team: established for hospitals where stroke units are not available. This is a team consisting of differnet professionals who treat stroke patients throughout the hospital wherever the patients may be.

The combined acute-rehabilitation stroke units have shown best results. In 23 trials with 4911 patients a significant (18%) mortality reduction, 23% reduction in dependence on other people's help and 25% reduction in the need of institutional care were recorded in comparison with patients treated at general wards.

The main indications for admission to acute stroke unit are:

– acute stroke with symptoms manifesting for less than 24 hours
– unstable or progressive neurologic deficit
– need of specific therapy (thrombolysis)
– need of early rehabilitation

The favorable results recorded at stroke unit probably are due to the fact that the needs of acute stroke patients can be met across different phases of the disease. A well organized stroke unit should meet all stroke patient needs during the emergency, acute and subacute phases of the disease.

During the emergency phase within the first 6-12 h of stroke onset, focus should be on the diagnosis and reduction of brain injury. In the acute phase from 12 to 72 h, focus should be on complication prevention, early mobilization, and start of rehabilitation. In the subacute phase from day 3 to day 14, the care is focused on rehabilitation combined with prevention of complications as well as prevention of new strokes and other vascular events.

The processes of Care in Stroke Units (evidence based)

Acute care and monitoring

Medical assessment

Medical history and examination
- biochemistry
- hematology

JLMU: Odjeli koji primaju akutne bolesnike, ali ih i rano otpuštaju (unutar 7 dana); bez respiratora i invazivnog monitoriranja, opremljeni uređajima za stalno kardijalno monitoriranje. Mali naglasak na rehabilitaciji.

Kombinirane akutno-rehabilitacijske jedinice: Specijalni odjel koji prihvaća bolesnike za akutno liječenje. Rano se započinje s mobilizacijom i rehabilitacijom, boravak 1-2 tjedna.

Mobilni timovi: Multidisciplinski timovi organizirani su za bolesnika s moždanim udarom za ustanove u kojima nije moguće organizirati JLMU.

Najbolje rezultate pokazale su kombinirane akutno-rehabilitacijske jedinice. Ukupno je bilo ispitano 4911 bolesnika u 23 randomizirane studije. Rezultati studija pokazali su smanjenje smrtnosti prema općim odjelima za 18%, potrebe za tuđom pomoći za 29%, potrebe za trajnim smještajem za 25%, dok je dužina liječenja skraćena za 30%.

Indikacije za liječenje u JLMU su slijedeće:

– akutni moždani udar sa simptomima ne dužim od 24 h
– nestabilni ili progresivni neurološki deficit
– potreba za specifičnim liječenjem (tromboliza)
– potreba za ranom rehabilitacijom

Dobri rezultati liječenja bolesnika u JLMU vjerojatno su u tome što ispunjavaju sve potrebe bolesnika s moždanim udarom u raznim fazama liječenja.

Dobro organizirana JLMU mora zadovoljiti sve potrebe bolesnika za vrijeme hitne, akutne i subakutne faze. Za vrijeme hitne faze (između 6 i 12 sati od nastanka moždanog udara) težište je na dijagnozi i smanjenju moždanog oštećenja. U akutnoj fazi od 12 do 72 sata od početka bolesti prioritet je sprječavanje komplikacija, rana mobilizacija i početak rehabilitacije. U subakutnoj fazi od 3. do 14. dana bolesti provodi se rehabilitacija i prevencija komplikacija, kao i prevencija recidiva cerebrovaskularnog inzulta i drugih vaskularnih zbivanja.

Zbrinjavanje bolesnika u JLMU (zasnovano na dokazima)

Akutno zbrinjavanje i monitoriranje

Medicinsko zbrinjavanje

Anamneza i klinički pregled
- biokemijski testovi
- hematološki testovi
- EKG
- CT

Selektivne pretrage
- UZV karotida
- UZV srca

- ECG
- CT scanning

Selective examinations

- carotid doppler US
- echocardiography

Nursing assessment

- vital signs
- care needs
- swallowing testing
- fluid balance
- pressure area risks
- monitoring of neurologic deficit
- therapy assesssment
- deterioration
- disablity

Early Managment

Medical assessment

- careful management of fluid/food (often i. v. saline solutions over first 12-24 h)
- antibiotics for suspected infection
- paracetamol for pyrexia
- oxygen (if hypoxia, drowsiness, cardiorespiratory disease)
- insulin (if hyperglycemia)
- blood pressure control in selected patients
- ongoing rehabilitation

Nursing assessment

- early mobilization
- careful positioning and handling
- pressure area care
- avoid urinary catheters

Ongoing rehabilitation

- early goal setting
- early involvement in rehabilitation
- provision of information
- close linking of nursing and rehabilitation
- discharge plans – cooperation with primary health care

Praćenje i njega

- vitalni znakovi
- njega
- test gutanja
- unos i iznos tekućine
- prevencija dekubitusa
- praćenje neurološkog deficita
- procjena liječenja
- pogoršanje
- neurološki deficit

Rano zbrinjavanje

Medicinsko zbrinjavanje

- pažljivo praćenje unosa tekućine/hrane (često i.v. otopina soli u prvih 12-24 sata)
- antibiotici (infekcija)
- paracetamol kod povišene tjelesne temperature
- kisik (hipoksija, omaglice, kardiorespiracijska bolest)
- inzulin (hiperglikemija)
- praćenje krvnog tlaka
- rehabilitacija
- rana mobilizacija
- pažljivo namještanje bolesnika
- česta promjena položaja
- prevencija dekubitusa
- izbjegavati urinarni kateter

Rehabilitacija

- rano postavljanje ciljeva
- rano uključivanje u proces rehabilitacije
- učinkovita razmjena informacija
- povezanost njege i rehabilitacije
- planiranje otpusta – suradnja s primarnom zdravstvenom zaštitom

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TREATMENT OF ELEVATED BLOOD PRESSURE IN ACUTE STROKE
LIJEČENJE POVIŠENOG KRVNOG TLAKA U AKUTNOM MOŽDANOM UDARU

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Elevated blood pressure takes the unenviable leading position at all lists of risk factors for either ischemic or hemorrhagic stroke. It was just the successful treatment of arterial hypertension that probably contributed most to reduction in the incidence of stroke.

Definition of Hypertension (WHO)

Optimal blood pressure	systolic <120 mm Hg, diastolic <80 mm Hg
Normal blood pressure	systolic <130 mm Hg, diastolic <85 mm Hg
Elevated blood pressure – hypertension	systolic <140 mm Hg, diastolic <90 mm Hg

Treatment of Hypertension (WHO)

Lifestyle modifications

- diuretics, beta blockers, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, vasodilatators

Currently, antihypertensive therapy implies specific and individualized therapy adjusted to each individual patient, taking into account age and presence of other risk factors (lipids, diabetes mellitus, atrial fibrillation, left ventricular hypertrophy) as well as previous vascular diseases (stroke, myocardial infarction) and other comorbidities (renal artery stenosis, asthma).

How to Treat Hypertension?

Nonpharmacologic Management – Lifestyle Modifications

- quit smoking
- weight loss
- reduced alcohol intake
- reduced salt intake
- increase in physical activity
- other dietary measures (greater intake of fish and vegetables, reduced intake of saturated fat)

Na svim listama čimbenika rizika za nastanak ishemijskog i hemoragijskog moždanog udara (MU) povišen tlak uvijek zauzima nezahvalno prvo mjesto. Upravo je uspješno liječenje arterijske hipertenzije bilo vjerojatno jedan od vodećih razloga za smanjenu incidenciju MU.

Definicija povišenog krvnog tlaka (SZO)

Optimalni tlak	sistolički <120 mm Hg, dijastolički <80 mm Hg
Normalni tlak	sistolički <130 mm Hg, dijastolički <85 mm Hg
Povišen tlak – hipertenzija	sistolički >140 mm Hg, dijastolički >90 mm Hg

Liječenje povišenog krvnog tlaka (SZO)

Mijenjanje životnih navika

- smanjenje tjelesne težine, prestanak pušenja, tjelovježba, smanjen unos soli, održavanje odgovarajućeg unosa kalija, kalcija i magnezija

Farmakološko liječenje

- diuretici, beta blokatori, inhibitori ACE, blokatori kalcijevih kanala, antagonisti angiotenzinskih receptora, vazodilatatori

Suvremeno poimanje antihipertenzivne terapije odnosi se na specifičnu i individualnu terapiju prilagođenu svakom bolesniku, uzimajući pritom u obzir dob i prisutnost drugih čimbenika rizika (lipidi, šećerna bolest, atrijska fibrilacija, hipertrofija lijeve klijetke), ali i ranijih vaskularnih bolesti (MU, srčani infarkt) te napokon i drugih komorbidnih čimbenika (stenoza bubrežne arterije, astma).

Kako liječiti povišen krvni tlak?

Nefarmakološko liječenje – promjena životnih navika

- prestanak pušenja
- smanjenje tjelesne težine
- smanjenje unosa alkohola
- smanjenje unosa soli

Pharmacologic Therapy

- all 6 classes of antihypertensive agents are efficient in blood pressure lowering and can be used as first choice medication
- dual combinations of antihypertensives from different classes have been recommended and found wide application in clinical practice
- AB/CD protocol

Blood Pressure Lowering Drugs

1) Alfa-adrenergic receptor blockers – a-blockers

There are no randomized data for drugs like prazosin and doxazosin, labetalol was investigated in a small study, and only doxazosin (Tonocardin) is commercially available in Croatia.

2) Angiotensin convertase enzyme inhibitors – ACE inhibitors

A small randomized trial has shown perindopril to lower elevated blood pressure by 11% without affecting general cerebral flow or MBFV in the middle cerebral artery. This group of antihypertensives is now one of the most commonly prescribed drug classes because of their relatively good effects and low rate of adverse events. The Croatian Institute of Health Insurance (CIHI) list of drugs includes enalapril (Enazil, Enap, Olivin), lisinopril (Irumed), perindopril (Prexanil), ramipril (Tritace), cilazapril (Cilazil), fosinopril (Monopril) and trandolapril (Gopten).

3) Angiotensin receptor antagonists – AT1 antagonists

ACCESS, a randomized study (unpublished, discontinued), showed candesartan to influence stroke outcome in terms of lower mortality and disability. The CIHI list includes losartan (Cozaar), valsartan (Diovan) and telmisartan (Pritor).

4) Beta-adrenergic receptor blockers – b-***blockers***

There is only one study demonstrating a tendency of the disease and outcome deterioration in patients administered atenolol or propranolol. Earlier, these drugs were considered a gold standard in the management of hypertension. In Croatia, oxprenolol (Trasicor), propranolol (Propranolol), atenolol (Ormidol, Atenolol, Tenormin), bisoprolol (Concor) and carvedilol (Carvetrend, Carvelol) are commercially available.

5) Calcium antagonists

Calcium antagonists are definitely the most commonly prescribed group of antihypertensives. Studies have shown calcium antagonists administered in the initial stage of stroke or later during stroke management failed to pro-

- povećana tjelesna aktivnost
- ostale prehrambene mjere (više ribe i povrća, manje zasićenih masnoća)

Farmakološko liječenje

- svih 6 skupina antihipertenziva učinkovito snižavaju krvni tlak i mogu biti prvi lijek izbora
- preporučene su i u kliničkoj praksi "uhodane" mnoge dvojne kombinacije antihipertenziva iz različitih skupina
- protokol AB/CD

Lijekovi za snižavanje krvnog tlaka

1) Blokatori alfa adrenergičnih receptora (alfa blokatori)

Nema randomiziranih podataka za lijekove poput prazosina i doksazosina, labetalol je istražen u maloj studiji, a u Hrvatskoj na tržištu je samo doksazosin (Tonocardin).

2) Inhibitori enzima angiotenzin konvertaze (inhibitori ACE)

Malo randomizirano istraživanje pokazalo je da perindopril snižava povišen krvni tlak za 11%, ali bez mijenjanja globalnog cerebralnog protoka ili SBSK u srednjoj moždanoj arteriji. Ova skupina antihipertenziva danas spada među one koje se najviše primjenjuju zbog razmjerno dobrog učinka i niskog postotka neželjenog djelovanja. Na listi lijekova HZZO-a nalaze se enalapril (Enazil, Enap, Olivin), lizinopril (Irumed), perindopril (Prexanil), ramipril (Tritace), cilazapril (Cilazil), fosinopril (Monopril), trandolapril (Gopten).

3) Blokatori angiotenzinskih receptora (AT1 antagonisti)

Jedno randomizirano istraživanje (neobjavljeno, prekinuto) pokazalo je utjecaj kandesartana na ishod moždanog udara u smislu manje smrtnosti i invaliditeta (studija ACCESS).

Na listi lijekova HZZO-a nalaze se losartan (Cozaar), valsartan (Diovan), telmisartan (Pritor).

4) Blokatori beta adrenergičnih receptora (beta blokatori)

Postoji tek jedno istraživanje koje je pokazalo trend pogoršanju stanja i ishoda bolesnika koji uzimaju atenolol ili propranolol. Ranije su predstavljali zlatni standard u liječenju hipertenzije. Na našem tržištu nalaze se oksprenolol (Trasicor), propranolol (Propranolol), atenolol (Ormidol, Atenolol, Tenormin), bisoprolol (Concor), karvedilol (Carvetrend, Carvelol).

duce any change in the patient functional outcome. The CIHI list includes amlodipine (Norvasc, Amlopin, Amonex), nifedipine (Nifedipin, Cordipin), lacidipine (Lacipil), verapamil (Isoptin) and diltiazem (Diltiazem, Aldizem).

6) Diuretics

These are inexpensive and efficacious antihypertensives, however, as yet without appropriate randomized clinical trials of their efficacy in terms of stroke outcome. In Croatia, furosemide (Fursemid, Edemid), spironolactone (Aldactone, Priul), chlorthalidone (Hygroton), indapamide (Tertensif, Amoron), triamteren with hydrochlorothiazide (Tiaren) and amyloride with hydrochlorothiazide (Moduretic) are available.

7) Vasodilatators – nitrates

These agents are rarely used for the treatment of elevated blood pressure in stroke. In Croatia, glyceryl trinitrate (Angised, Nitrolingual, Trinitrosan, Nitronal), isosorbide dinitrate (Tinidil) and isosorbide mononitrate (Olicard, manufactured by ISMN Genericon or Jadran) are commercially available. Two small randomized trials have shown the transdermally applied glyceryl trinitrate to decrease blood pressure by 6%-8% without affecting BFV.

AB/CD Rule
(Dickerson *et al.*, University of Cambridge, UK; Lancet 1999)

A – ACE inhibitors, B – Beta blockers,
C – Ca antagonists, D – Diuretics

1) monotherapy: age £55 A or B
   age £55 C or D
2) dual combination: A + B or C + D
3) triple combination: A + C + D or B + C + D
   add alfa blocker to A + B or C + D combination
4) consider specialist consultation for arterial hypertension
   Shortcoming: angiotensin receptor blockers (AT1 antagonists) are ignored.

Treatment of Hypertension in Acute Stroke

The majority of patients have elevated blood pressure during the first few hours of stroke onset. Blood pressure may be elevated for a number of reasons such as:

- pre-existing arterial hypertension
- neuroendocrine system activation

5) Antagonisti kalcija

Među antihipertenzivnim lijekovima zasigurno skupina koja se najčešće propisuje. Provedena istraživanja pokazala su pak kako antagonisti kalcija primjenjivani odmah na početku MU ili kasnije tijekom liječenja nisu promijenili funkcionalni ishod kod bolesnika. Na listi HZZO-a nalaze se amlodipin (Norvasc, Amlopin, Amonex), nifedipin (Nifedipin, Cordipin), lacidipin (Lacipil), verapamil (Isoptin) i diltiazem (Diltiazem, Aldizem).

6) Diuretici

Ovo su jeftini i učinkoviti antihipertenzivi zasad bez odgovarajućih randomiziranih kliničkih ispitivanja što se tiče učinkovitosti za ishod liječenja MU. Na našem tržištu nalaze se furosemid (Fursemid, Edemid), spironolakton (Aldactone, Priul), klortalidon (Hygroton), indapamid (Tertensif, Amoron), triamteren sa hidroklortiazidom (Tiaren), amilorid s hidroklortiazidom (Moduretic).

7) Vazodilatatori - nitrati

Ovi lijekovi se rijetko rabe u liječenju povišenog krvnog tlaka u MU. Na tržištu u Hrvatskoj nalazimo gliceril trinitrat (Angised, Nitrolingual, Trinitrosan, Nitronal), zatim izosorbid dinitrat (Tinidil) te izosorbid mononitrat (Olicard, ISMN Genericon ili Jadran). Dva mala randomdizirana ispitivanja pokazala su kako transdermalno aplici-ran gliceril trinitrat smanjuje krvni tlak za 6%-8% bez mijenjanja BSK.

Pravilo AB/CD (Dickerson *et al*., University of Cambridge, UK, Lancet 1999.)
Primjena antihipertenzivne terapije i kombinacije antihipertenziva u 4 stupnja:

A – ACE inhibitori, B – Beta blokatori,
C – Ca antagonisti, D – Diuretici

1) monoterapija: mlađi od 55 godina A ili B
   stariji od 55 godina C ili D
2) dvostruka kombinacija: A + B ili C + D
3) trostruka kombinacija: A + C + D ili B + C + D
   dodati alfa blokator kombinaciji A + B ili C + D
4) razmisliti o konzultiranju specijalista za arterijsku hipertenziju
   Nedostatak: ignoriranje blokatora angiotenzisnskih receptora, AT1 antagonista.

Liječenje povišenog krvnog tlaka u moždanom udaru

Najveći broj bolesnika imaju povišen krvi tlak tijekom prvih sati nakon moždanog udara. Tlak može biti povišen

- pain
- nausea, vomiting
- elevated intracranial pressure (Cushing's reflex)
- restlessness and disorientation
- anxiety
- stress due to stroke
- full bladder
- physiologic response to hypoxia

Also, elevated blood pressure may act as a compensatory mechanism to maintain adequate cerebral perfusion.

In ischemic stroke, cerebral autoregulation is impaired. In this case, the brain needs elevated blood pressure, and abrupt blood pressure reduction may result in deterioration of the neurologic deficit. Elevated blood pressure is present in more than 75%-80% of stroke patients (International Stroke Trial – IST, Lancet 1997).

Blood pressure is generally higher in patients with primary cerebral hemorrhage in comparison with ischemic stroke patients.

Blood pressure will usually spontaneously resume prestroke values in about a week, however, it may remain elevated in one third of stroke patients.

The value of blood pressure at the onset of stroke may be directly connected to stroke outcome. Greatly elevated or decreased blood pressure increases the risk of death and disability, as demonstrated in a number of small studies as well as in meta-analyses. Small studies point to the fact that Ca blockers, ACE inhibitors and nitrates but not thiazide diuretics cause acute blood pressure decrease.

On the other hand, subsequent longterm antihypertensive therapy as a secondary prevention of stroke should be taken in consideration in all patients with hypertension.

Scientific research and clinical trials on stroke treatment are now primarily focused on reperfusion and neuroprotection, while neglecting the need of homeostasis regulation, which firstly refers to the management of hypertension, hyperglycemia, hyperpyrexia and cerebral edema. Each of these factors is associated with aggravated outcome of stroke.

Large studies to investigate the rationale for blood pressure lowering in the acute stage of stroke are expected to be launched or are just under way.

Main dilemma: to treat or not to treat hypertension in acute stroke?

The physicians managing acute stroke patients are daily faced with this serious dilemma.

Unfortunately, definite evidence to help them decide are greatly lacking.

zbog mnogo razloga, na primjer:

- od ranije postojeća arterijska hipertenzija
- aktiviranje neuroendokrinog sustava
- bol
- mučnina, povraćanje
- povećan intrakranijski tlak (Cushingov refleks)
- nemir i dezorijentacija
- tjeskoba
- stres od moždanog udara
- pun mokraćni mjehur
- fiziološki odgovor na hipoksiju

Isto tako povišen krvni tlak može biti kompenzacijski mehanizam za održavanje odgovarajuće moždane perfuzije.

Prilikom ishemijskog moždanog udara dolazi do poremećaja moždane autoregulacije. U tim slučajevima mozgu je potreban povišen krvni tlak i naglo snižavanje tlaka može rezultirati pogoršanjem neurološkog deficita. Povišen krvni tlak prisutan je kod više od 75%-80% bolesnika s MU (International Stroke Trial – IST, Lancet 1997.).

Krvni tlak pretežno je viši kod bolesnika s primarnim moždanim krvarenjem u usporedbi s ishemijskim MU.

Obično se tlak spontano regulira nakon prvog tjedna, iako kod trećine bolesnika i dalje ostaje povišen.

Vrijednost krvnog tlaka pri nastupu moždanog udara može biti izravno povezana s njegovim ishodom. Izrazito povišen ili pak nizak krvni tlak povećava rizik od smrti i invalidnosti, što je pokazano u mnogim manjim studijama ali i u meta-analizama.

Manje studije ukazuju na činjenicu da blokatori Ca, inhibitori ACE i nitrati akutno snižavaju krvni tlak, ali ne i tijazidski diuretici.

S druge strane, za sve bolesnike s povišenim tlakom treba uzeti u obzir potrebu za kasnijom dugotrajnom antihipertenzivnom terapijom u smislu sekundarne prevencije MU.

Znanstvena istraživanja i klinički pokusi u liječenju moždanog udara danas su prvenstveno usredotočeni na reperfuziju i neurozaštitu, a zanemaruje se potreba regulacije homeostaze, što se prvenstveno odnosi na liječenje povišenog krvnog tlaka, hiperglikemije, hiperpireksije, moždanog edema. Svaki taj čimbenik povezan je s pogoršanjem ishoda MU.

Očekuju se ili su u tijeku velike studije koje istražuju ima li smisla snižavati krvni tlak u akutnoj fazi MU.

Glavna dvojba: treba li liječiti povišen krvni tlak u akutnom MU ili ne?

Liječnici koji liječe bolesnike u akutnoj fazi MU svakodnevno su suočeni s tom ozbiljnom dvojbom. Nažalost,

In the absence of evidence to rely on, it is no surprise that there are quite controversial opinions on how to manage blood pressure in acute stroke.

Most common questions:

- introduction of antihypertensive therapy
- continuation or discontinuation of antihypertensive therapy the patient was taking prior to stroke
- blood pressure increase

Those advocating blood pressure reduction are primarily influenced by the evidence indicating that blood pressure lowering is the most efficient strategy in both primary prevention and in secondary prevention in patients with cerebrovascular disease.

On the other hand, those giving preference to discontinuation of antihypertensive therapy and recommending blood pressure increase explain it by the need to maintain cerebral perfusion thus to reduce cerebral ischemia.

A useful contribution to this debate is found in the report on ACCESS (Acute Candesartan Citexetil Therapy in Stroke Survivors, Stroke 2003), a randomized, double blind, placebo controlled study designed so as to investigate the safety of moderate blood pressure lowering by the administration of candesartan to patients with hypertension (BP >180-200/105-110 mm Hg) over the first 36 hours of acute ischemic stroke. The primary ACCESS end-points (death and disability at 3 months) showed no difference between the two patient groups, whereas secondary end-points (death, recurrent stroke, cardiac complications, and disability at 12 months) showed a significant, 48% reduction (odds ratio = 0.48) in the group of patients administered candesartan. These results confirmed the drug efficacy in stroke, as previously also demonstrated in myocardial ischemia, although the mechanism of action has not yet been elucidated. The study was discontinued at that point.

There have been a number of small studies of blood pressure lowering in acute stroke using all groups of hypertensives. Some studies have shown a favorable effect in ischemic stroke and cerebral hemorrhage, whereas others point to unfavorable outcomes. Yet, these mostly were not large, properly designed and randomized studies, thus the data could not be considered relevant and reliable enough to contribute to the assessment of the need of blood pressure management in stroke.

Besides large clinical trials, additional pathophysiology studies are also needed to investigate the effect of blood pressure modification on cerebral circulation and hemostasis in various types of stroke by use of, e.g., PET

postoji izrazit manjak primjerenih dokaza koji bi utjecali na njihove odluke.

U odsutnosti dokaza na koje se stručnjak može zasigurno osloniti ne iznenađuje to što postoje potpuno različita mišljenja o tome kako postupati s krvnim tlakom u akutnom MU.

Najčešća pitanja:

- uvođenje antihipertenzivne terapije
- nastavak ili prekid antihipertenzivne terapije koju je bolesnik uzimao prije MU
- pitanje podizanja krvnog tlaka

Oni koji zastupaju tezu spuštanja krvnog tlaka pod utjecajem su prvenstveno dokaza da je spuštanje krvnog tlaka najdjelotvornija strategija kako u primarnoj prevenciji tako i u sekundarnoj prevenciji u bolesnika s cerebrovaskularnom bolešću.

S druge pak strane oni koji zagovaraju prestanak antihipertenzivne terapije i preporučuju povišenje krvnog tlaka objašnjavaju to potrebom za održavanjem moždane perfuzije i time smanjenjem moždane ishemije.

Koristan doprinos ovoj raspravi možemo naći u studiji ACCESS (Acute Candesartan Citexetil Therapy in Stroke Survivors – Stroke 2003), randomiziranoj, dvostruko slijepoj, placebom kontroliranoj studiji zamišljenoj tako da se ispita sigurnost umjerenog snižavanja krvnog tlaka davanjem kandesartana bolesnicima s hipertenzijom (RR >180 -200/105-110) u prvih 36 h od akutnog ishemijskog MU. Studija ACCESS: primarni krajnji ishod (smrt i invaliditet, nakon 3 mjeseca) nije pokazao razliku među dvjema skupinama, dok je sekundarni krajni ishod (smrt, recidiv MU, srčane komplikacije, invaliditet, nakon 12 mjeseci) pokazao značajno smanjenje za 48% (odds ratio = 0,48) u skupini bolesnika koji su dobivali kandesartan. Time je potvrđena djelotvornost u MU koja je ranije za isti lijek dokazana i za ishemiju miokarda, iako mehanizam djelovanja nije razjašnjen. U toj je fazi studija prekinuta.

Učinjeno je i mnogo malih pokusa o snižavanju krvnog tlaka u akutnoj fazi MU, a rabljene su sve skupine antihipertenziva. Neke studije pokazale su povoljan učinak u ishemijskom MU i moždanom krvarenju, dok su druge pokazale škodljive ishode. Ipak, u većini slučajeva ne radi se o velikim, dobro dizajniranim i randomiziranim pokusima, dakle, niti o relevatnim podacima koji bi dali koristan doprinos u procjeni potrebe liječenja krvnog tlaka u MU.

Uz velike kliničke studije potrebne su i daljnje patofiziološke studije koje će istražiti učinak promjena krvnog tlaka na moždani protok i hemostazu u različitim tipovima MU, na primjer, primjena PET (*positron emission tomo-*

(positron emission tomography), SPECT (single photon emission CT), TCD, perfusion and diffusion MR (with evaluation of penumbra, mismatch), quantitative perfusion CT and xenon CT.

Recommendations for Blood Pressure Management in Acute Stroke

1) International Society of Hypertension (ISH)
2) American Stroke Association (ASA)
3) European Stroke Initiative (EUSI)
4) Ministry of Health of the Republic of Croatia

1) International Society of Hypertension (ISH)

Statement on the Management of Blood Pressure in Acute Stroke (J Hypertens 2003)

Current clinical practice: various published guidelines are not evidence based and differ in recommendations for the treatment of hypertension in patients with acute stroke who have not received thrombolytic therapy. Although not consistent with evidence based medicine, there is quite a strong consensus suggesting that elevated blood pressure should be lowered in patients with cerebral hemorrhage in order to reduce the risk of hematoma increase or recurrent hemorrhage. It is suggested that extremely high blood pressure (>200/120 mm Hg) in patients with cerebral hemorrhage should be actively lowered. The latest guidelines emphasize the need of blood pressure relative modification (e.g., reduction by 20% in cerebral hemorrhage).

Proposal for future studies: considering the fact that for the time being there are no completed large studies investigating the safety and efficacy of blood pressure modification in acute stroke, the neurologists dealing with cerebrovascular diseases 'cry out' for evidence based medicine answers to the following questions:

- should blood pressure be lowered in acute ischemic stroke? – this question is not only important *per se* but also because the recommendations for thrombolytic therapy suggest that blood pressure be monitored during the treatment with alteplase;
- should blood pressure be increased in acute ischemic stroke when there is evidence for hypoperfusion?
- should blood pressure be lowered in cerebral hemorrhage?
- should previous antihypertensive therapy be continued or temporarily interrupted?
- what type or combination of antihypertensives should be used?

graphy), SPECT (*single photon emission* CT), TCD, perfuzijske i difuzijske MR (s procjenom penumbre, *mismatch*), kvantitativne perfuzijske CT i ksenon CT.

Preporuke za regulaciju krvnog tlaka u akutnom moždanom udaru

1) International Society of Hypertension (ISH)
2) American Stroke Association (ASA)
3) European Stroke Initiative (EUSI)
4) Ministarstvo zdravstva RH

1) International Society of Hypertension (ISH)

Statement on the Management of Blood Pressure in Acute Stroke (J Hypertens, 2003.)

Sadašnja klinička praksa: aktualne objavljene smjernice nisu temeljene na dokazima i međusobno se razlikuju u savjetima kako liječiti povišen tlak u bolesnika s akutnim MU koji nisu dobili trombolitičnu terapiju. Iako se ovdje ne radi o medicini zasnovanoj na dokazima, postoji prilično jak konsenzus o tome da povišen krvni tlak treba sniziti u bolesnika s moždanim krvarenjem radi smanjenja rizika od povećanja hematoma ili ponovnog krvarenja. Savjetuje se da bolesnicima s izrazito povišenim krvnim tlakom (>200/120 mm Hg) u moždanom krvarenju krvni tlak treba aktivno snižavati. Posljednje smjernice naglašavaju potrebu promjene krvnog tlaka u relativnim razmjerima (na primjer, sniženje za 20% u moždanom krvarenju).

Preporuke za buduća istraživanja: kako zasad nema završenih velikih studija sigurnosti i djelotvornosti mijenjanja krvnog tlaka u akutnom MU, tako i neurolozi koji se bave cerebovaskularnim bolestima "vape" za slijedećim odgovorima temeljenim na medicini zasnovanoj na dokazima:

- treba li snižavati krvni tlak u akutnom ishemijskom MU? – ovo pitanje nije važno samo po sebi, nego i stoga što preporuke za trombolitičnu terapiju navode kako treba pratiti krvni tlak tijekom terapije pomoću alteplaze
- treba li povisivati krvni tlak u akutnom ishemijskom MU kada postoji dokaz za hipoperfuziji?
- treba li snižavati krvni tlak u moždanom krvarenju?
- treba li nastaviti prethodnu antihipertenzivnu terapiju ili ju privremeno obustaviti?
- koju vrstu ili kombinaciju antihipertenziva treba rabiti?
- kada započeti s liječenjem?
- koliko mora krvni tlak biti povišen?
- koja je ekonomska opravdanost liječenja krvnog tlaka?

- when to initiate antihypertensive therapy?
- to what level should blood pressure be increased?
- what is the cost effectiveness of blood pressure therapy?

Such future trials and research studies should include representative patient groups selected according to the following parameters:

- demographic characteristics
- blood pressure values
- pre-existence of arterial hypertension or coronary disease
- stroke type
- stroke severity
- size of brain lesion

Some studies of such a design are just under way or planned to start:

- COSSACS: Continue Or Stop post-Stroke Antihypertensive Collaborative Study, launched in 2003
- CHHIPS: Hypotension Immediately Post-Stroke, ongoing
- ENOS: Efficacy of Nitric Oxide in Stroke, ongoing
- IMAGES: Intravenous Magnesium Efficacy in Stroke, ongoing

ISH Conclusions:

- elevated blood pressure (>140/90 mm Hg) is very common (in ~75% of patients) early after ischemic stroke, however, its possible effect on functional recovery has not yet been definitely identified
- elevated blood pressure is very common (>80%) after cerebral hemorrhage and is associated with a poor outcome
- low blood pressure values (<120/80 mm Hg) are rare (5%)
- 50% of stroke patients receive antihypertensive therapy
- the lack of large studies entails general uncertainty concerning blood pressure management in ischemic or hemorrhagic stroke
- optimal treatment of blood pressure in acute stroke remains obscure, therefore there is a great need of large, randomized studies

2) Stroke Council of the American Stroke Association (ASA)

Guidelines for Early Management of Patients with Ischemic Stroke

Takve buduće studije i istraživanja morati će sadržavati reprezentativne skupine bolesnika prema:

- demografskim značajkama (dob, spol, narodnost)
- vrijednostima krvnog tlaka
- postojanju prethodne arterijske hipertenzije ili koronarne bolesti
- vrsti MU
- težini MU
- veličini lezije mozga

Nekoliko takvih istraživanja su u tijeku ili se planiraju:

- COSSACS – Continue Or Stop post-Stroke Antihypertensive Collaborative Study, započinje 2003.
- CHHIPS – Hypotension Immediately Post-Stroke, u tijeku
- ENOS – Efficacy of Nitric Oxide in Stroke, u tijeku
- IMAGES – Intravenous Magnesium Efficacy in Stroke, u tijeku

Zaključci ISH:

- povišen krvni tlak (>140/90) vrlo je čest (otprilike u 75% bolesnika) rano nakon ishemijskog MU i zasad nije sa sigurnošću utvrđeno ima li utjecaja na funkcionalni oporavak
- povišen krvni tlak je vrlo čest (>80%) nakon moždanog krvarenja i povezan je s lošim ishodom
- niske vrijednosti krvnog tlaka (<120/80 mm Hg) su rijetke (5%)
- 50% bolesnika s MU prima antihipertenzivnu terapiju
- nedostatak velikih pokusa dovodi do globalne nesigurnosti glede stava o liječenju krvnog tlaka u ishemijskom ili hemoragijskom MU
- optimalno liječenje krvnog tlaka u akutnom MU ostaje nepoznato i postoji velika potreba za randomiziranim i velikim studijama

2) Smjernice za rano liječenje bolesnika s ishemijskim moždanim udarom

Vijeća za moždani udar Američke asocijacije za moždani udar *(Stroke Council of the American Stroke Association, ASA)*

Prve preporuke za liječenje ishemijskog MU ASA je objavila 1994. godine. Nakon što je Uprava za hranu i lijekove (*Food and Drug Administration*) odobrila primjenu rekombiniranog tkivnog aktivatora plazminogena (rtPA) izdane su nove, usklađene preporuke 1996. godine.

Činjenice: nedostatak pouzdanih podataka i studija, dosadašnji rezultati proturječni, nema znanstvenog pokrića ni klinički dokazane koristi od snižavanja krvnog tlaka, kod

The first ASA guidelines for the treatment of ischemic stroke were published in 1994. The guidelines were revised in 1996, upon FDA had issued approval for recombinant tissue plasminogen activator (rtPA).

Facts: lack of reliable data and studies; controversial results reported to date; no scientific basis or clinically demonstrated benefit of blood pressure reduction; in most patients, blood pressure declines spontaneously without any specific medical therapy; optimal treatment of blood pressure in acute stroke has not been determined.

"... in most circumstances, the blood pressure should generally not be lowered ..."

Although severe hypertension can be considered as an indicator for treatment, there are no data on defined blood pressure values that would require urgent treatment.

Yet, there is a consensus that antihypertensive agents should be prescribed when systolic blood pressure is >220 mm Hg or diastolic blood pressure >120 mm Hg.

The following conditions may require urgent antihypertensive therapy in acute stroke:

- hypertensive encephalopathy
- dissection of aorta
- acute renal insufficiency
- acute pulmonary edema
- acute myocardial infarction

Along with general therapeutic measures, the patient should be placed in a quiet room, his bladder should be voided, pain control should be introduced, and the possibly elevated intracranial pressure should be lowered. May an indication for antihypertensive therapy be made, blood pressure should be lowered with caution. In patients treated with thrombolytic agents continuous blood pressure monitoring and possibly due correction should be done during rtPA administration and for the next 24 hours because of the risk of complications in terms of cerebral hemorrhage. Thrombolytic therapy should not be used if systolic pressure is >185 mm Hg or diastolic pressure >110 mm Hg.

Approach to elevated blood pressure in acute stroke

A) without thrombolytic therapy:

systolic BP <220 mm Hg or diastolic BP <120 mm Hg

- observation, monitoring
- treatment of other possible organ diseases
- treatment of other stroke symptoms (headache, vomiting, elevated intracranial pressure, epileptic seizures, hypoglycemia)

većine bolesnika krvni tlak se spontano snižava bez specifične medicinske terapije, optimalno liječenje krvnog tlaka u akutnom MU nije utvrđeno,

" ... u većini situacija krvni tlak uglavnom ne treba snižavati …"

Iako se teška hipertenzija može smatrati indikacijom za liječenje, nema podataka o definiranim vrijednostima krvnog tlaka koji bi zahtijevali hitno liječenje.

Ipak postoji konsenzus o tome da antihipertenzivne lijekove treba ordinirati onda kad je sistolički tlak >220 mm Hg ili dijastolički tlak 120 mm Hg.

Stanja koja također mogu zahtijevati hitnu antihipertenzivnu terapiju u akutnom MU su

- hipertenzivna encefalopatija
- aortna disekcija
- akutna bubrežna insuficijencija
- akutni plućni edem
- akutni infarkt miokarda

Također, uz opće mjere liječenja bolesnika treba smjestiti u tihu sobu, isprazniti mu mjehur, kontrolirati bol, sniziti eventualno povišen intrakranijski tlak. Ako postavi indikacija za antihipertenzivnu terapiju, spuštanje krvnog tlaka treba oprezno provoditi. Kod bolesnika koji se liječe trombolitičnim sredstvima potrebno je stalno praćenje tlaka i eventualno ispravljanje i to tijekom davanja rtPA i kroz prva 24 sata zbog opasnosti od komplikacija u smislu moždanog krvarenja. Trombolitičnu terapiju ne davati ako je sistolički RR >185 mm Hg ili dijastolički >110 mm Hg.

Pristup povišenom krvnom tlaku u akutnom MU

A) bez trombolitične terapije

sistolički RR <220 ili dijastolički <120

- opservacija, praćenje
- tretirati eventualne bolesti drugih organa
- liječiti druge simptome MU (glavobolja, povraćanje, povišen intrakranijski tlak, epileptični napadaji, hipoglikemija)

sistolički RR >220 ili dijastolički >120

- labetalol 10-20 mg i.v. kroz 1-2 minute (može se ponavljati svakih 10 minuta do maksimalne doze od 300 mg)
- nikardipin 5 mg/h i.v. kao početna doza (titrirati do željenog učinka povećavajući dozu za 2,5 mg/h svakih 5 minuta do najviše 15 mg/h

dijastolički >140

- nitroprusid 0,5 mg/kg/min i.v. infuzija kao početna doza uza stalno praćenje RR

systolic BP >220 mm Hg or diastolic BP >120 mm Hg
- labetalol 10-20 mg i.v. over 1-2 min (can be repeated every 10 minutes up to the maximal dose of 300 mg)
- nicardipine 5 mg/h i.v. as initial dose (titrated to the desirable effect by increasing the dose by 2.5 mg/h every 5 minutes up to the maximal dose of 15 mg/h)

diastolic BP >140 mm Hg
- nitroprusside 0.5 mg/kg/min i.v. infusion as initial dose with continuous BP monitoring

B) with thrombolytic therapy:
systolic BP >185 mm Hg or diastolic BP >110 mm Hg
- labetalol 10-20 mg i.v. over 1-2 minutes, then repeat it or administer 1-2 inches of Nitropast (if blood pressure does not fall to a satisfactory level, the use of rtPA should be discontinued)
- in case of elevated blood pressure values observed on monitoring a patient who has received thrombolytic therapy, labetalol or nicardipine should be administered as described above, and nitroprusside should be initiated as necessary

3) European Stroke Initiative (EUSI) Recommendations for Stroke Management – Update 2003 (Cerebrovasc Dis 2003)

Blood pressure monitoring and treatment are important because many patients with acute stroke have elevated blood pressure. Some data are in favor of blood pressure treatment, however, there also is evidence against it. A target systolic blood pressure of 180 mm Hg and diastolic blood pressure of 100-105 mm Hg is advised in patients with pre-existing hypertension. In other cases, desirable blood pressure levels are 160-180/90-100 mm Hg. Clearly, extremely high blood pressure values are not acceptable (although values of up to 240/130 mm Hg are accepted in the USA). A systolic blood pressure of >220 mm Hg or diastolic blood pressure of >120 mm Hg is an indication for early but cautious use of antihypertensives while avoiding abrupt and massive blood pressure reduction.

In case of concomitant diseases such as acute myocardial infarction, cardiac insufficiency, acute renal insufficiency, aortic arch dissection, blood pressure reduction is also desirable.

In patients receiving thrombolytic or heparin therapy blood pressure levels higher than 180 mm Hg should be avoided.

In intracerebral hematoma, subdural hematoma and subdural hemorrhage, elevated blood pressure should also be properly treated.

B) s trombolitičnom terapijom
sistolički >185 mm Hg ili dijastolički >110 mm Hg
- labetalol 10-20 mg i.v. kroz 1-2 minute, ponoviti ili Nitropasta 1-2 inča (ako krvni tlak ne padne na zadovoljavajuće vrijednosti, treba odustati od primjene rtPA)
- tijekom praćenja bolesnika koji je primio trombolitičnu terapiju u slučaju povišenih vrijednosti RR da vati labetalol ili nikardipin kako je opisano, prema potrebi započeti i s nitroprusidom

3. European Stroke Initiative (EUSI) Recommendations for Stroke Management – Update 2003 (Cerebrovascular Dis 2003.)

Praćenje i liječenje krvnog tlaka važni su jer mnogi bolesnici s akutnim MU imaju povišen krvni tlak. Neki podaci govore u prilog tom liječenju, ali postoje i dokazi protiv njega. Ciljni sistolički krvni tlak od 180 mm Hg i dijastolički od 100-105 mm Hg preporučuju se kod bolesnika s prethodnom hipertenzijom. U drugim slučajevima poželjne vrijednosti krvnog tlaka su 160-180/90-100 mm Hg. Očito ekstremno visoke vrijednosti nisu prihvatljive (iako se u SAD prihvaćaju i vrijednosti do 240-130 mm Hg). Sistolički krvni tlak >220 mm Hg ili dijastolički >120 mm Hg predstavljaju indikaciju za ranu ali opreznu upotrebu antihipertenziva, izbjegavajući naglo i jako rušenje vrijednosti krvnog tlaka.

U slučaju supostojećih bolesti, npr. akutni infarkt miokarda, srčana insuficijencija, akutna bubrežna insuficijencija, disekcija luka aorte, poželjno je također spuštanje vrijednosti krvnog tlaka.

Kod bolesnika koji primaju trombolitičnu ili heparinsku terapiju trebalo bi izbjegavati krvni tlak viši od 180 mm Hg.

Kod intracerebralnih hematoma, subduralnih hematoma, kao i kod subarahnoidnih krvarenja također se liječe povišene vrijednosti krvnog tlaka.

Antihipertenzivi koji se mogu rabiti u akutnom MU:

inhibitor ACE – kaptopril 6-12,5 mg s.c.
središnji simpatikolitik – klonidin 0,075 mg s.c. ili 0,2 mg in. i potom 0,1 mg/h (do 0,8 mg) i.v.
vazodilatatori – nitroprusid 0,25-10 mg/kg min. i.v.
– nitroglicerin 5-100 mg/kg min. i.v.
– dihidralazin 6,5-20 mg i.v. bolus i.v.
Beta blokator – propranolol 1-10 mg i.v.
Alfa blokator – labetalol 20-80 mg bolus i.v. i potom 2 mg/min. i.v. infuzija

The following antihypertensives can be used in stroke patients:

ACE inhibitor – captopril 6-12.5 mg s.c.

central sympaticolytic – clonidine 0.075 mg s.c. or 0.2 mg in., then 0.1 mg/h (up to 0.8 mg) i.v.

vasodilatators – nitroprusside 0.25-10 mg/kg/min i.v.
– nitroglycerin 5-100 mg/kg/min i.v.
– dihydralazine 6.5-20 mg bolus i.v.

beta-blocker – propranolol 1-10 mg i.v.

alfa-blockers – labetalol 20-80 mg bolus i.v., then 2 mg/min i.v. infusion
– urapidil 10-50 mg bolus i.v., then 9-30 mg/h i.v. infusion

4. Ministry of Health of the Republic of Croatia Guidelines for Stroke Treatment

Developed by the expert team headed by Professor Vida Demarin, M.D., Ph.D.; available at the Ministry of Health web sites.

Considering elevated blood pressure management, these guidelines are consistent with EUSI guidelines.

– urapidil 10-50 mg bolus i.v. i potom 9-30 mg/h i.v. infuzija

4. Smjernice za liječenje moždanog udara Ministarstva zdravstva Republike Hrvatske

Sastavio ekspertni tim na čelu s Prof. dr. Vidom Demarin – nalaze se na web stranicama Ministarstva zdravstva RH.

Glede liječenja povišenog krvnog tlaka, u svim odrednicama su sukladne smjernicama EUSI.

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NEW MODALITIES IN THE TREATMENT OF STROKE
NOVOSTI U LIJEČENJU MOŽDANOG UDARA

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Introduction

Any report on stroke treatment modalities should start with listing the following major risk factors for stroke that are liable to modification:

- arterial hypertension
- diabetes mellitus
- dyslipidemia
- nonvalvular atrial fibrillation
- carotid stenosis
- smoking
- obesity
- physical inactivity

The possibilities of acute stroke treatment are still quite limited. Taking the term of treatment in a broad sense, preventive approach remains the most efficient method of treatment, i.e. elimination or modification of the above listed risk factors. A rise in diastolic arterial pressure by 7 mm Hg or systolic pressure by 12 mm Hg has been demonstrated to increase the risk of stroke by 50%! Thus, the number of strokes in the USA could theoretically be reduced by 360,000 cases *per* year with efficacious treatment of arterial hypertension[1].

A number of large clinical studies have recently been completed which have in part or completely changed some concepts of the treatment and prevention of stroke, especially considering anticoagulation and antiaggregation therapy as well as the use of particular procedures of interventional radiology. Some of these studies have enabled better understanding and more efficacious management of the above listed risk factors. In addition, a number of clinical studies that have just been under way have already produced some guidelines for the treatment and prevention of stroke.

Anticoagulation (Antithrombotic) Agents in Stroke Prevention

A meta-analysis of five large randomized clinical studies of the use of coumarin in nonvalvular atrial fibrillation

Uvod

Svako izlaganje o modalitetima liječenja moždanog udara moralo bi započeti nabrajanjem osnovnih rizičnih čimbenika moždanog udara podložnih modifikaciji, a to su:

- arterijska hipertenzija
- šećerna bolest
- dislipidemija
- nevalvularna atrijska fibrilacija
- karotidna stenoza
- pušenje
- debljina
- tjelesna neaktivnost

Naime, mogućnosti liječenja akutnog moždanog udara još uvijek su značajno ograničene. Shvatimo li pojam liječenja u širem smislu, onda možemo kazati da je zasad najučinkovitija metoda liječenja moždanog udara preventivni pristup – tj. uklanjanje ili modificiranje prije nabrojenih čimbenika rizika. Dokazano je da porast dijastolnog arterijskog tlaka za 7 mm Hg – ili sistolnog tlaka za 12 mm Hg – podiže rizik moždanog udara za 50%! Tako bi se – teoretski – učinkovitim liječenjem arterijske hipertenzije broj moždanih udara u SAD mogao umanjiti za 360.000 slučajeva na godinu[1].

Nedavno je završen niz velikih kliničkih studija koje su dijelom ili u cijelosti promijenile određena stajališta u liječenju i prevenciji moždanog udara, osobito u pogledu antikoagulacijskog i antiagregacijskog liječenja, kao i primjene određenih postupaka intevencijske radiologije. Neke od tih studija omogućile su bolje razumijevanje i učinkovitije liječenje prije nabrojenih čimbenika rizika. Konačno, niz kliničkih istraživanja koja su trenutno u tijeku već sada daju određene smjernice za liječenje i prevenciju moždanog udara.

Antikoagulantna (antitrombotska) sredstva u prevenciji moždanog udara

Metaanaliza pet velikih randomiziranih kliničkih istraživanja primjene kumarina u nevalvularnoj atrijskoj

(NVAF) has led to a conclusion that the use of coumarin for NVAF resulted in 68% stroke risk reduction as compared with the control group. Although the same meta-analysis confirmed the efficacy of acetylsalicylic acid (ASA) in the prevention of stroke in NVAF patients, the risk reduction with the use of ASA for this indication did not exceed 20%. Coumaring is obviously the most efficacious agent for prevention of stroke in patients with NVAF.

It has been generally accepted that coumarin is indicated for all NVAF patients if exhibiting some of the following stroke risk factors:

- previous history of stroke, transient ischemic attack (TIA) or systemic embolism
- arterial hypertension
- congestive cardiomyopathy
- age ≥75 years
- impaired function of the left chamber

Considering efficacious daily dose of coumarin, it is variably determined for various indications. The target INR values are as follows:

- nonvalvular atrial fibrillation INR 2-3, lifelong
- left chamber thrombus INR 2-3, 3-6 months
- acute myocardial infarction INR 2-3, 6 months
- artificial valve INR 3-4, lifelong

In the meantime, ximelagatran, a new peroral direct thrombin inhibitor, has appeared on the market. This drug has some advantages over coumarin:

- greater therapeutic range
- no need of dose calibration or INR control
- interactions of ximelagatran with food or other drugs are very rare

Comparison of the efficacy of ximelagatran and coumarin in NVAF was investigated in two clinical studies, SPORTIF III and SPORTIF V. These were randomized clinical trials comparing adapted doses of warfarin (target INR 2-3) and fixed dose of ximelagatran (2x36 mg/day) in risk patients with NVAF[2]. SPORTIF III was an open-label study, whereas SPORTIF V was designed as a double-blind study. The primary study endpoint was stroke or systemic embolism. In brief, the studies produced the following results (note: negative value – better ximelagatran):

- SPORTIF III: – 0.66% (95% CI, –1.4% to 0.1%)
- SPORTIF V: +0.45% (95% CI, –0.1% to 1.1%)
- meta-analysis: – 0.03% (95% CI, –0.6% to 0.6%)

As for possible complications, the rate of hemorrhage was lower with the administration of ximelagatran (SPOR-

fibrilaciji (NVAF) rezultirala je zaključkom da se primjenom kumarina u NVAF postiže 68%-tno sniženje rizika za moždani udar u odnosu na kontrolnu skupinu. Premda je ista metaanaliza potvrdila da je acetilsalicilna kiselina (ASK) također učinkovita u prevenciji moždanog udara u bolesnika s NVAF, postignuto smanjenje rizika uz primjenu ASK za tu indikaciju dostizalo je najviše 20%. Kumarin je očito najučinkovitije sredstvo prevencije moždanog udara u osoba s NVAF.

Prema opće prihvaćenom stajalištu kumarin je indiciran za sve bolesnike s NVAF ako iskazuju još jedan od slijedećih čimbenika rizika za moždani udar:

- prethodni moždani udar, TIA ili sistemska embolija
- arterijska hipertenzija
- kongestivna kardiomiopatija
- životna dob ≥75 godina
- oslabljena funkcija lijeve komore

Učinkovita dnevna doze kumarina određuje se drukčije za različite indikacije. Ciljne vrijednosti INR-a su slijedeće:

- nevalvularna AF INR 2-3, doživotno
- tromb lijeve komore INR 2-3, 3-6 mjeseci
- akutni infarkt miokarda INR 2-3, 6 mjeseci
- umjetna valvula INR 3-4, doživotno

U međuvremenu na tržistu se je pojavio novi peroralni izravni inhibitor trombina, ksimelagatran. U odnosu na kumarin, ovaj lijek posjeduje određene prednosti:

- veću terapijsku širinu
- nema potrebe za baždarenjem doze ili za nadzorom INR
- interakcije ksimelagatrana s hranom ili drugim lijekovima vrlo su rijetke

Usporedba učinkovitosti ksimelagatrana i kumarina u NVAF bila je tema dviju kliničkih studija, SPORTIF III. i SPORTIF V. To su bili randomizirani klinički pokusi usporedbe prilagođene doze varfarina (ciljna vrijednost INR-a 2-3) i fiksne doze ksimelagatrana (2x36 mg na dan) u rizičnih bolesnika s NVAF[2]. SPORTIF III. bila je tzv. otvorena studija, dok je SPORTIF V. zamišljena kao dvostruko slijepo ispitivanje. Primarni cilj studije bio je moždani udar ili sistemska embolija.

Rezultati studija bili su slijedeći (napomena: negativna vrijednost – bolji ksimelagatran):

- SPORTIF III.: – 0,66% (95% CI, – 1,4% do 0,1%)
- SPORTIF V.: +0,45% (95% CI, – 0,1% do 1,1%)
- Metaanaliza: – 0,03% (95% CI, – 0,6% do 0,6%)

U pogledu mogućih komplikacija, učestalost krvarenja bila je niža kod primjene ksimelagatrana (SPORTIF III.:

TIF III: 25.5% *vs.* 29.5%; SPORTIF V: 37% *vs.* 47%), whereas liver function tests showed greater deviation with the use of ximelagatran (6.1% *vs.* 0.8%).

If we accept that coumarin is the most efficacious agent available for patients at a high risk of cardioembolic stroke, it appears logical to pose the following question: How to treat patients with stroke due to microvascular disease or patients with atherothrombotic stroke as part of aortic arch macrovascular disease or those with cryptogenic stroke, i.e. a stroke without clear etiology? Is anticoagulation therapy also indicated for prevention of these stroke types?

The WARSS (Warfarin *vs.* Aspirin Recurrent Stroke Study) trial was so designed as to address this goal, i.e. to answer the question of anticoagulation therapy efficacy in patients with noncardioembolic stroke[3]. It was a multicenter, double-blind, randomized, clinical study of secondary prevention of stroke. The study included 2206 patients with noncardioembolic ischemic stroke, randomized into two groups. One group received coumarin (adapted dose, INR 1.4-2.8), and the other group received ASA 325 mg/day for 2 years. The primary endpoint was stroke or death. None of the study subgroups (lacunar stroke, atherothrombotic stroke, patients with antiphospholipid syndrome) had better prognosis with warfarin. The stroke risk quotient was 1.13 (coumarin *vs.* ASA), and the rate of hemorrhage was 2.22 and 1.49 *per* 100 patient-years for coumarin and ASA, respectively. Thus, besides lower efficacy, coumarin was associated with a considerably higher rate of complications.

Another interesting study related to the efficacy of coumarin and ASA for this indication was WASID (Warfarin Aspirin Symptomatic Intracranial Disease Trial)[4]. The criterion for patient selection was symptomatic disease of great intracranial arteries (>50% stenosis of ICA, MCA, vertebral or basilar artery). A total of 569 study patients were administered coumarin (target INR 2-3) or ASA at a dose of 1300 mg/day. The study was discontinued for safety reasons, as no difference in the stroke risk reduction was observed, whereas lethal outcome was recorded in 10% of patients on coumarin *vs.* 4% of patients administered ASA. Major hemorrhage was observed in 8% and 3% of patients on coumarin and ASA, respectively.

Antiaggregation Agents in Stroke Prevention

While the efficacy of antiaggregation agents in the prevention and treatment of stroke is unquestionable, many questions are still a matter of discussion and subject of numerous clinical studies. ACE study (Aspirin for patients undergoing Carotid Endarterectomy) appears to be of

25,5% prema 29,5%, SPORTIF V.: 37% prema 47%), dok su testovi jetrenih funkcija pokazali značajnija odstupanja kod primjene ksimelagatrana (6,1% prema 0,8%).

Prihvatimo li tvrdnju da je kumarin najučinkovitije raspoloživo sredstvo za bolesnike s visokim rizikom od kardioembolijskog moždanog udara, postavlja se logično pitanje: Kako liječiti bolesnike s moždanim udarom uzrok kojega je bolest malih krvnih žila ili bolesnike s aterotrombotskim moždanim udarom u sklopu bolesti velikih krvnih žila aortnog luka, kao i bolesnike s kriptogenim moždanim udarom – tj. moždanim udarom bez jasne etiologije? Je li antikoagulantno liječenje indicirano i za prevenciju ovih vidova moždanog udara?

S tim je ciljem zamišljena studija WARSS (*Warfarin vs. Aspirin Recurrent Stroke Study*) koja je trebala odgovoriti na pitanje učinkovitosti antikoagulacijskog liječenja u bolesnika s s ne-kardioembolijskim moždanim udarom[3]. Radilo se o multicenričnom, dvostruko slijepom randomiziranom kliničkom istraživanju sekundarne prevencije moždanog udara. Bilo je uključeno 2206 bolesnika s ne-kardioembolijskim ishemijskim moždanim udarom, koji su randomizirani u dvije skupine. Jedna je skupina primala kumarin (prilagođena doza, INR 1,4-2,8), a druga ASK 325 mg na dan tijekom 2 godine. Primarni krajnji ishod studije bio je moždani udar ili smrt. Nijedna od ispitnih podskupina (lakunarni moždani udar, aterotrombotski moždani udar, bolesnici s antifosfolipidnim sindromom) nije imala bolju prognozu s varfarinom. Kvocijent rizika za moždani udar iznosio je 1,13 (kumarin prema ASK), a učestalost krvarenja bila je 2,22 na 100 bolesnik-godina za kumarin prema 1,49 za ASK. Dakle, uz manju učinkovitost kumarin je imao i znatno veću učestalost komplikacija.

Slijedeća zanimljiva studija vezana za odnos učinkovitosti kumarina i ASK u ovoj indikaciji je WASID (*Warfarin Aspirin Symptomatic Intracranial Disease Trial*)[4]. Kriterij izbora ispitanika bila je simptomatska bolest velikih intrakranijskih arterija (>50%-tno suženje ICA, MCA, vertebralne ili bazilarne arterije). Ukupno je bilo uključeno 569 ispitanika koji su primali kumarin (ciljna vrijednost INR-a 2-3) ili ASK u dozi od 1300 mg na dan. Studija je prekinuta zbog sigurnosnih razloga. Naime, nije utvrđena nikakva razlika u smanjenju rizika za moždani udar, no smrtni ishod zabilježen je u 10% bolesnika na kumarinu u odnosu na isti ishod u 4% bolesnika koji su primali ASK. Značajnije krvarenje opaženo je u 8% bolesnika na kumarinu u odnosu na 3% bolesnika koji su primali ASK.

special interest. It was a randomized clinical trial including 3000 patients submitted to carotid endarterectomy[5]. This study has answered a question open for a long time now, i.e. since the discovery of the antiaggregation properties of ASA: What is the optimal dose of ASA in the prevention of stroke? Study subjects received one of the 4 ASA doses during the perioperative period: 81 mg, 325 mg, 650 mg or 130 mg *per* day. As the results recorded in subjects receiving lower doses (81 and 325 mg) and in those on higher doses (650 and 1300 mg) of ASA were similar, the original four groups were finally reduced to two groups. Then, the subjects on either of the lower doses (81 or 325 mg) of ASA showed a significantly lower rate of complications including stroke, myocardial infarction and death. Thus, the conclusion derived from the study was that ASA doses higher than 325 mg/day for stroke prevention were not justifiable.

The next study related to antiaggregation agents was ESPS-2 (European Stroke Prevention Study 2), a multicenter, randomized, double-blind, placebo controlled study aimed at assessing the efficacy of ASA, dipyridamole, and a combination of the two in the prevention of stroke[6]. The study included subjects who had sustained TIA or ischemic stroke within 3 months prior to inclusion in the study, with a 2-year follow-up period. Study subjects were divided into four groups randomized to any of the following treatment protocols:

- 200 mg extended release dipyridamole (ER-DP) twice daily
- 25 mg ASA twice daily
- 25 mg ASA + 200 mg ER-DP twice daily
- placebo twice daily

Results of this study indicated that, although both ASA and dipyridamole are efficacious antiaggregation agents in stroke prevention, the combination of the two showed additional efficacy, i.e. a synergistic action of these two antiaggregation agents. This was the first clinical study demonstrating the biologic value of the combination of these two antiaggregation agents with different mechanisms of action.

Clopidogrel, a novel antiaggregation drug, has recently appeared on the market. Comparison of the efficacy of this drug with ASA as an established antiaggregation agent was simply unavoidable. The topic was addressed in the CAPRIE study (Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events)[7], a prospective, randomized, double-blind clinical study that included 19,185 patients with atherosclerotic vascular disease from 304 hospital

Antiagregacijska sredstva u prevenciji moždanog udara

Premda je učinkovitost antiagregacijskih sredstava u prevenciji i liječenju moždanog udara nesporna, mnoga su pitanja još uvijek predmet rasprava i cilj brojnih kliničkih istraživanja. Posebno je zanimljiva studija ACE (*Aspirin for patients undergoing Carotid Endarterectomy*), randomizirano kliničko istraživanje kojim je bilo obuhvaćeno 3000 bolesnika koji su podvrgnuti karotidnoj endarterektomiji[5]. Naime, ova nam je studija pružila odgovor na pitanje koje se provlači već dugi niz godina, tj. otkako su otkrivena antiagregacijska svojstva acetilasilicilne kiseline: koja je optimalna doza ASK u prevenciji moždanog udara?

Ispitanici su primali jednu od 4 moguće doze ASK tijekom perioperacijskog razdoblja: 81 mg, 325 mg, 650 mg ili 1300 mg na dan. S obzirom na to da su rezultati u ispitanika koji su primali niže doze (81 i 325 mg), kao i rezultati ispitanika na višim dozama (650 i 1300 mg) ASK bili slični, četiri ishodišne skupine konačno su svedene na dvije. Ispitanici koji su primali neku od nižih doza (81 ili 325 mg) imali su značajno manju učestalost komplikacija u smislu moždanog udara, infarkta miokarda ili smrti. Stoga je i zaključak studije slijedeći: doze ASK više od 325 mg na dan u cilju prevencije moždanog udara nemaju opravdanja.

Slijedeća studija vezana za antiagregacijska sredstva je ESPS-2 (*European Stroke Prevention Study 2*), multicentrično, randomizirano, dvostruko slijepo, placebom kontrolirano istraživanje cilj kojega je bila procjena učinkovitosti ASK, dipiridamola, te kombinacije ovih dvaju lijekova u prevenciji moždanog udara[6]. Uključeni su bili ispitanici koji su preboljeli TIA ili ishemijski moždani udar unutar 3 mjeseca prije uključivanja u studiju. Praćenje je trajalo dvije godine, a ispitanici su podijeljeni u četiri skupine kojima je dodijeljena jedna od slijedećih shema liječenja:

- 200 mg dipiridamola s produljenim otpuštanjem (ER-DP) dva puta na dan
- 25 mg ASK dva puta na dan
- 25 mg ASK + 200 mg ER-DP dva puta na dan
- placebo dva puta na dan

Rezultati ovoga istraživanja ukazali su na činjenicu da, premda su i ASK i dipiridamol učinkovita antiagregacijska sredstva u prevenciji moždanog udara – kombinacija ovih dvaju lijekova posjeduje dodatnu učinkovitost, tj. da se radi o sinergizmu ovih dvaju antiagregacijskih sredstava. Ovo je ujedno i prvo kliničko istraživanje koje je dokazalo biološku vrijednost kombinacije dvaju antiagregacijskih sredstava različitih mehanizama djelovanja.

Tablica 1. ESPS-2: relative risk reduction according to groups

Therapy	Stroke	Stroke or death
ERDP +ASK prema placebu	37%	24%
ERDP prema placebu	16%	15%
ASK prema placebu	18%	13%

centers. The stroke subgroup included patients with prior stroke within the last 6 months before entering the study. Randomized patient groups were administered clopidogrel at a dose of 75 mg or ASA at a dose of 325 mg for up to 3 years (mean 1.6 years). Although the results of this study suggested a slight preference to be given to clopidogrel (the rate of recurrent stroke lower by 8.7% than with ASA), the true question is: Is the combination of ASA and clopidogrel more efficient in the prevention of stroke than the individual action of either agent?

This question was answered by the CURE study (Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndrome), a prospective, randomized, double-blind clinical trial that included 12,562 patients with acute coronary syndrome[8]. The study primary endpoints were cardiovascular death, myocardial infarction or stroke. Study subjects received either of two combinations: ASA (75-325 mg/day) + placebo or ASA + 75 mg clopidogrel. The treatment was continued for at least 12 months. This combination (ASA + clopidogrel) also proved more efficacious than ASA alone, this by 20% on an average for all study endpoints.

A number of large studies of antiaggregation therapy are still under way, thus their results have not yet become available. However, mention should be made of the SPS3 study (Secondary Prevention of Small Subcortical Strokes), a randomized, 2x2 factorial trial, planning to include a total of 2500 patients with small subcortical infarcts. This clinical trial, sponsored by the American NIH (National Institutes of Health), has been designed at two levels. At the first level, ASA alone, and ASA + clopidogrel combination are compared, whereas the second level will compare the usual arterial blood pressure control (target values of systolic blood pressure, 130-149 mm Hg) and intensive control arterial blood pressure (systolic pressure, £129 mm Hg).

Another study just about to be completed is PRoFESS (Prevention Regimen for Effectively Avoiding Second Stroke), a randomized, double-blind, 2x2 factorial study

Table 1. ESPS-2: relativno smanjenje rizika u pojedinim skupinama

Terapija	Moždani udar	Moždani udar ili smrt
ERDP +ASK prema placebu	37%	24%
ERDP prema placebu	16%	15%
ASK prema placebu	18%	13%

Relativno nedavno na tržištu se je pojavio i novi antiagregacijski lijek, klopidrogel. Usporedba učinkovitosti ovoga lijeka s etabliranim antiagregacijskim sredstvom – ASK – bila je neizbježna. Ova je tema obrađena u studiji CAPRIE (*Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events*)[7]. Radilo se je o prospektivnom, randomiziranom, dvostruko slijepom kliničkom istraživanju kojim je bilo obuhvaćeno 19.185 bolesnika s aterosklerotskom bolešću krvnih žila u 304 bolnička centra. U podskupinu moždanog udara bili su uključeni bolesnici koji su preboljeli moždani udar unutar 6 mjeseci prije uključivanja. Radnomizirane skupine primale su klopidogrel u dozi od 75 mg ili ASK u dozi od 325 mg. Liječenje je trajalo do 3 godine (prosječno 1,6 godina).

Premda su rezultati ove studije dali blagu prednost klopidrogelu (8,7% manja učestalost novog moždanog udara u odnosu na ASK), pravo je pitanje slijedeće: predstavlja li kombinacija ASK i klopidrogela učinkovitije sredstvo u prevenciji moždanog udara u odnosu na njihovu pojedinačnu djelotvornost?

Na to je pitanje odgovorila studija CURE (*Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndrome*), prospektivno, randomizirano, dvostruko slijepo kliničko istraživanje kojim je bilo obuhvaćeno 12.562 ispitanika s akutnim koronarnim sindromom[8]. Primarni ishodi studije bili su kardiovaskularna smrt, infarkt miokarda ili moždani udar. Ispitanici su primali jednu od dviju kombinacija: ASK (75-325 mg na dan) + placebo ili kombinaciju ASK + 75 mg klopidrogela. Liječenje je trajalo najmanje 12 mjeseci. I ova je kombinacija (ASK + klopidrogel) bila učinkovitija od primjene same ASK, i to prosječno oko 20% za sve moguće ishode.

Neke od velikih studija vezane za antiagregacijske lijekove još su u tijeku, te nam rezultati nisu dostupni. Iz te skupine izdvajam studiju SPS3 (*Secondary Prevention of Small Subcortical Strokes*), randomizirani 2x2 čimbenski pokus kojim se planira obuhvatiti ukupno 2.500 bolesnika s malim subkortikalnim infarktima. Ovo kliničko istraži-

Table 2. CURE: prevalence of death and stroke in study groups

	ASK + placebo	ASK + klopidrogel		
		%	RR	CI
Broj ispitanika	6.303	6.259		
Kardiovaskularna smrt	11,41%	9,30%	0,80	0,72-0,90
Moždani udar	1,38%	1,20%	0,86	0,63-1,18

Tablica 2. CURE: učestalost smrti i moždanog udara u ispitnim skupinama

	ASK + placebo	ASK + klopidrogel		
		%	RR	CI
Broj ispitanika	6.303	6.259		
Kardiovaskularna smrt	11,41%	9,30%	0,80	0,72-0,90
Moždani udar	1,38%	1,20%	0,86	0,63-1,18

comparing a combination of clopidogrel and ASA with dipyridamole, and telmisartan with placebo. The study includes 15,500 subjects, and the results will be published towards the end of 2004.

Surgical Therapy for Carotid Diseases

The classic NASCET study (Surgical Endarterectomy for Extracranial Carotid Disease) is best known in the field. The study included subjects with >70% symptomatic carotid stenosis[9]. Study subjects were randomized to a group on medicamentous therapy and a group treated with surgical therapy. Over a 2-year period, ipsilateral stroke occurred 26% of medicamentously treated and 9% of surgically treated patients. Less favorable results, yet better in medicamentously treated patients, were obtained in the subgroup with 5%-69% symptomatic carotid stenosis. Poorer results were recorded in asymptomatic patients with carotid stenosis irrespective of the degree of stenosis. The following perioperative complications posed a problem:

- death or stroke 5.8%
- cranial nerve lesion 7.6%
- hematoma 5.5%
- wound infection 3.4%
- cardiac complications 4.0%

These complications were the reason for ever more frequent attempts at using the methods of interventional radiology for stroke prevention. There have been a number of randomized clinical studies of the use of carotid stenting.

CAVATAS (Carotid & Vertebral Artery Transluminal Angioplasty Study) was a multicenter, randomized, clinical study comparing endovascular stent and carotid endarterectomy in the management of carotid stenosis[10]. The study includes 504 patients with carotid stenosis (96% with symptomatic disease) followed-up for 3 years. In the group treated with endovascular technique, stent was placed in 26% and balloon angioplasty was performed in the remaining 74% of patients. Angioplalsty and/or stent-

vanje koje sponzorira američki NIH (*National Institutes of Health*) zamišljeno je na dvjema razinama. U prvoj se provodi usporedba djelotvornosti same ASK i kombinacije ASK i klopidogrela, dok se u drugoj želi usporediti uobičajenu kontrolu visine arterijskog tlaka (ciljne vrijednosti sistolnog tlaka od 130-149 mm Hg) i intenzivni nadzor arterijskog tlaka (sistolni tlak 129 mm Hg ili manje).

Slijedeća studija koja je pred završetkom je PRoFESS (*Prevention Regimen for Effectively Avoiding Second Strokes*), randomizirani, dvostruko slijepi, 2x2 čimbenski pokus usporedbe kombinacije klopidogrela i ASK s dipiridamolom, te usporedbe telmisartana i placeba. Studijom je obuhvaćeno 15.500 ispitanika, a rezultati će biti objavljeni krajem ove (2004.) godine.

Kirurško liječenje bolesti karotida

U ovom je području najpoznatija već klasična studija NASCET (*Surgical Endarterectomy for Extracranial Carotid Disease*) kojom su obuhvaćeni ispitanici sa simptomatskom stenozom karotide višom od 70%[9]. Ispitanici su randomizirani u skupinu koja je liječena medikamentno i u kirurški liječenu skupinu. Ipsilateralni moždani udar doživjelo je tijekom razdoblja od dvije godine 26% medikamentno liječnih ispitanika u odnosu na 9% kirurški liječenih bolesnika. Bolesnici sa simptomatskom stenozom karotide od 50%-69% imali su slabije rezultate, premda još uvijek bolje od medikamentno liječenih bolesnika, dok su za asimptomatske bolesnike sa stenozom karotide bez obzira na stupanj suženja rezultati bili još lošiji. Problem su predstavljale perioperacijske komplikacije:

- smrt ili moždani udar 5,8%
- lezija kranijskog živca 7,6%
- hematom 5,5%
- infekcija rane 3,4%
- srčane komplikacije 4,0%

Upravo su navedene komplikacije bile razlogom sve češćih pokušaja primjene metoda interventne radiologije

ing proved technically successful in 89% of cases. The rate of stroke recurrence and/or death during the first 30 days was comparable in the two groups (10%), whereas the rate of significant restenosis was considerably higher in the group treated with endovascular technique (14% *vs.* 4%).

CREST study (Cerebral Revascularization Endarterectomy *versus* Stenting) is a randomized clinical trial comparing endovascular techniques and carotid endarterectomy, anticipating to include 2500 subjects with >50% symptomatic carotid stenosis[11]. Study subjects have been followed-up for 4 years, and 691 patients were treated by stent technique till the end of 2003. The percentage of patients sustaining recurrent stroke or death was 3.5%, which is considerably lower than the expected proportion of these surgical procedure outcomes (6%-10%).

SSYLVIA (Stenting of Symptomatic Atherosclerotic Lesions in the Extracranial Vertebral and Intracranial Arteries) is an open-label study of angioplasty or stenting[12]. Inclusion criterion were symptomatic atherosclerotic stenoses of extracranial (vertebral) or intracranial arteries, whereas clinical follow-up took one year with repeat CAG at 6 months. Study subjects received clopidogrel for 4 weeks after angioplasty or stenting, then also ASA for one year. The study included 60 subjects from 12 centers, and has reported on 95% technical success (residual stenosis <50%). There was no death during the procedure, however, there were 4 cases of stroke during the first 30 days of intervention, and 4 cases of stroke during further follow-up (365 days). A relatively high rate of restenosis was observed, especially in case of ostial vertebral stenosis.

Conclusions

- New anticoagulation and antiaggregation agents allow for reliable protection of patients with risk factors for stroke (or for stroke recurrence).
- Novel endovascular interventional techniques are a promising option for some of these patients.
- The true potential of these methods has yet to be confirmed in clinical trials.

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u prevenciji moždanog udara. Postoji čitav niz randomiziranih kliničkih pokusa primjene karotidnog stenta.

CAVATAS (*Carotid & Vertebral Artery Transluminal Angioplasty study*) je multicentrično randomizirano kliničko istraživanje usporedbe endovaskularnog stenta i karotidne endarterektomije u liječenju suženja karotida[10]. U istraživanje je uključeno 504 bolesnika sa stenozom karotide (96% sa simptomatskom bolešću), koji su praćeni tijekom 3 godine. U skupini koja je liječena endovaskularnom tehnikom stent je postavljen u 26% ispitanika, dok je u preostalih 74% izvršena balon-angioplastika. Angioplastika i/ili stentiranje pokazali su se tehnički uspješnim u 89% slučajeva. Učestalost ponovnog moždanog udara i/ili smrti tijekom prvih 30 dana bila je podjednaka u objema skupinama (10%), dok je učestalost značajne restenoze bila znatno viša u endovaskularno liječenoj skupini (14% prema 4%).

Studija CREST (*Cerebral Revascularization Endarterectomy versus Stenting*) je randomizirano kliničko istraživanje usporedbe endovaskularnih tehnika i karotidne endarterektomije, kojim se planira obuhvatiti 2.500 ispitanika sa simptomatskim suženjem unutarnje karotide višim od 50%[11]. Ispitanici su praćeni tijekom 4 godine, a dosad (kraj 2003. godine) 691 bolesnik liječen je stent-tehnikom. Postotak bolesnika koji su doživjeli novi moždani udar ili su umrli tijekom zahvata iznosi 3,5%, što je znatno manje od očekivanog postotka takvog ishoda kirurškog zahvata (6%-10%).

SSYLVIA (*Stenting of Symptomatic Atherosclerotic Lesions in the Extracranial Vertebral and Intracranial Arteries*) je otvoren pokus angioplastike ili stentiranja[12]. Kriterij uključivanja su simptomatska aterosklerotska suženja na ekstrakranijskim (vertebralnim) ili intrakranijskim arterijama, a kliničko praćenje trajalo je godinu dana uz ponavljanje CAG nakon 6 mjeseci. Ispitanici su primali klopidogrel tijekom 4 tjedna nakon angioplastike ili stentiranja, te zatim i ASK tijekom godine dana. Uključeno je 60 ispitanika u 12 centara, a postignuto je 95% tehničkog uspjeha (ostatna stenoza manja od 50%). Smrt tijekom samog postupka nije zabilježena, no zabilježena su 4 slučaja moždanog udara tijekom prvih 30 dana nakon intervencije, te 4 slučaja moždanog udara tijekom daljnjeg praćenja (365 dana). Opažen je i relativno visok postotak ponovnih stenoza, osobito u slučaju ostijalnih vertebralnih suženja.

Zaključci

- Novi antikoagulacijski i antiagregacijski lijekovi omogućuju pouzdanu zaštitu bolesnika s čimbenicima rizika za moždani udar (ili za recidiv moždanog udara).

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- Nove endovaskularne interventne tehnike ohrabrujuće su rješenje za dio tih bolesnika.
- Stvarni potencijal tih metoda trenutno je još uvijek predmet kliničkih istraživanja.

THE ROLE OF NEW ANTIHYPERTENSIVE AND LIPID LOWERING DRUGS IN STROKE PREVENTION

ULOGA NOVIJIH ANTIHIPERTENZIVA I STATINA U PREVENCIJI MOŽDANOG UDARA

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Summary

Recently published data from large, randomized clinical trials show that lowering of blood pressure and elevated cholesterol reduction is associated with significant decrease in stoke risk. Besides blood pressure and cholesterol lowering it seems that the use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium antagonists (CA) and statins could provide some additional beneficial effects. ACEI and ARB could improve endothelial function, cardiac and vascular remodeling, thus retarding progression of atherosclerosis. CA, especially the highly lipophilic ones, may have some antioxidant properties. They reduce the oxidation of LDL and its influx into the arterial wall. Amlodipine, lacidipine or nifedipine suppress platelet production in hypertensive patients. Statins could have beneficial effects such as improvement of endothelial-dependent flow-mediated vasodilatation, modulating the inflammatory response, decreasing clot formation, and decreasing the adherence of platelets to the ruptured plaque thus stabilizing the atherosclerotic plaque. Other antiatherosclerotic properties of statins include reducing of accumulation of inflammatory cells in atherosclerotic plaques, inhibiting vascular smooth muscle cell proliferation, inhibiting platelet function, and improving of vascular endothelial function.

Key words: *treatment of hypertension, antihypertensives, treatment of hypercholesterolemia, statins*

Sažetak

Prema nedavno objavljenim podacima iz velikih randomiziranih kliničkih studija sniženje povišenog krvnog tlaka i sniženje povišenog kolesterola povezani su sa značajnim padom rizika za nastanak moždanog udara. Pretpostavlja se da primjena lijekova iz skupine inhibitora konvertaze angiotenzina (inhibitori ACE), blokatora angiotenzinskih receptora, antagonista kalcijevih kanala i statina ima uz regulaciju krvnog tlaka i sniženje serumskog kolesterola i neke dodatne povoljne učinke. Inhibitori ACE i blokatori angiotenzinskih receptora mogu poboljšati funkciju endotelnih stanica i usporiti napredovanje ateroskleroze. Antagonisti kalcijevih kanala, poglavito oni koji su izrazito lipofilni, imaju i neka antioksidacijska svojstva. Oni smanjuju oksidaciju čestica LDL i sprječavaju njihov ulazak u stijenke arterijskih krvnih žila. Amlodipin, lacidipin ili nifedipin suzbijaju stvaranje trombocita u hipertenzivnih bolesnika. Statini pospješuju vazodilataciju, utječu na upalni odgovor u endotelnim stanicama, smanjuju stvaranje krvnih ugrušaka i adheziju trombocita na rupturirani plak, te utječu na stabilizaciju aterosklerotskog plaka. Ostala antiaterosklerotska obilježja statina uključuju: smanjeno nakupljanje upalnih stanica u aterosklerotskom plaku, inhibiciju proliferacije glatkih mišićnih stanica krvne stijenke, inhibiciju funkcije trombocita i poboljšanje funkcije vaskularnih stanica endotela.

Ključne riječi: *hipertenzija, antihipertenzivi, hiperlipidemija, prevencija moždanog udara*

Introduction

Stroke is defined by the World Health Organization as a clinical syndrome of rapid onset of focal or global cerebral deficit, lasting for more than 24 h or leading to death, with no apparent cause other than a vascular one. Stroke could be ischemic, approximately 80%, or hemorrhagic, approximately 20% of all strokes in white populations. Stroke is a major public health burden worldwide. It is one of the three most common causes of death worldwide. Most of all strokes are probably due to changes that atherosclerosis produces on arterial tree and on the heart. Therefore, most conventional vascular risk factors for atherosclerosis are also considered as risk factors for stroke. Although there has been great improvement in stroke treatment in recent years, prevention of stroke still has a pivotal role in the approach to stroke[1,2].

In this paper results of clinical trials dealing with elevated blood pressure and elevated cholesterol plasma concentrations in stroke prevention are presented, with special emphasis on the potential new beneficial actions of some groups of antihypertensives (angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium antagonists (CA) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, i.e.statins.

Antihypertensive Treatment

Hypertension is one of the most potent risk factors for first ever and recurrent stroke. Lowering of blood pressure has been known for years to reduce the risk of a first stroke. Blood pressure lowering for primary prevention of stroke could be undertaken using a variety of therapeutic agents: beta-blockers, ACEI, ARB, CA, diuretics, etc. The choice of first line antihypertensive drug is still difficult.

ALLHAT trial showed in 33,357 participants with hypertension no difference in combined fatal coronary heart disease or nonfatal myocardial infarction between the groups treated with a thiazide diuretic chlorthalidone (12.5 to 25 mg/d), CA amlodipine (2.5 to 10 mg/d) or ACEI lisinopril (10 to 40 mg/d). The lisinopril group a had higher stroke rate than the chlorthalidone group (6.3% *vs* 5.6%). The authors suggest the use of thiazide diuretics because they are superior in preventing one or more major forms of cardiovascular disease and are less expensive. Therefore, they should be preferred as first-step antihypertensive therapy[3]. The PROGRESS trial showed the relative-risk reduction by about 25% to be associated with a decrease of 9 mm Hg in systolic and 4 mm Hg in diastolic blood

Uvod

Prema definiciji Svjetske zdravstvene organizacije, moždani udar je klinički sindrom vaskularne etiologije koji se očituje naglim nastankom žarišnog ili globalnog moždanog deficita što traje duže od 24 sata ili dovodi do smrtnog ishoda. Moždani udar je jedan od triju najčešćih uzroka smrti u svijetu i značajan javno-zdravstveni problem. Oko 80% svih moždanih udara uzrokovano je ishemijom (tromboza ili embolija), a oko 20% nastaje zbog hemoragije (intracerebralno krvarenje ili subarahnoidno krvarenje). Većina moždanih udara uzrokovana je aterosklerotskim promjenama na stijenkama arterija te bolestima srca. Stoga se brojni kardiovaskularni rizični čimbenici ubrajaju u rizične čimbenike za nastanak moždanog udara. Iako je posljednjih godina u liječenju moždanog udara postignut značajan napredak, prevencija je i nadalje najučinkovitija metoda za smanjivanje učestalosti moždanog udara[1,2]. Rezultati velikih kliničkih studija pokazuju kako snižavanje povišenog krvnog tlaka koje se postiže primjenom nekih skupina antihipertenziva (inhibitori konvertaze angiotenzina /inhibitori ACE/, blokatori angiotenzinskih receptora i antagonisti kalcijevih kanala), te snižavanje serumskog kolesterola primjenom statina (inibitori reduktaze 3-hidroksi-3-metil-glutaril koenzima-A /HMG-CoA/) imaju povoljan učinak u prevenciji moždanog udara.

Liječenje antihipertenzivima

Hipertenzija je jedan od najvažnijih čimbenika rizika za nastanak i recidiv moždanog udara. Snižavanje povišenog krvnog tlaka smanjuje rizik od nastanka moždanog udara. U primarnoj prevenciji moždanog udara postupak snižavanja krvnog tlaka postiže se primjenom različitih vrsta antihipertenziva (beta-blokatori, inhibitori ACE, antagonisti kalcijevih kanala, diuretici itd.), ali je lijek prvog izbora za liječenje hipertenzije još uvijek teško odrediti. Kliničke studije o antihipertenzivnoj terapiji uglavnom procjenjuju učestalost kardiovaskularnih incidenata kao mjeru uspješnosti terapije.

U studiji ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) uspoređivao se je učinak tiazidskog diuretika klortalidona (12.5-25 mg/dan), kalcijevog antagonista amlodipina (2.5-10 mg/dan) i inhibitora ACE lizinoprila (10-40 mg/dan). U skupini bolesnika koji su liječeni lizinoprilom stopa moždanog udara bila je viša u odnosu na klortalidonsku skupinu (6.3% *vs* 5.6%). Diuretici su se pokazali djelotvornijima u prevenciji većine kardiovaskularnih incidenata, a s obzirom na to

pressure[4]. In the PROGRESS trial a combination of perindopril and indapamide as well as perindopril alone were tested. The reduction in stroke risk was approximately of the size that could be predicted from epidemiological observations, meaning that there was probably no additional effect of the drugs tested over and above their blood pressure-lowering effect[2].

However, recent clinical evidence reveal ACEI as potent agents in preventing ischemic events and in blocking an array of ischemic processes, including atherogenesis[13]. It seems that ACEI and probably ARB could improve endothelial function, cardiac and vascular remodeling, retard the anatomic progression of atherosclerosis, and reduce the risk of myocardial infarction, stroke and cardiovascular death[5]. The first trial that showed other potential beneficial effects of ACEI beyond blood pressure reduction was Heart Outcomes Prevention Evaluation (HOPE). The HOPE trial showed in 9297 high-risk patients that lowering of systolic blood pressure by only 3.3 mm Hg and diastolic blood pressure by only 1.4 mm Hg using ramipril 10 mg once daily *per os* caused relative risk reduction of stroke by 32% compared with placebo. The high percentage of stroke risk reduction was supposed to be due to independent, additional effect of ramipril besides blood pressure lowering[6]. The Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE) did not show any difference in blood pressure lowering in 9193 participants aged 55-80 with essential hypertension between ARB losartan and beta blocker atenolol groups, but during the follow up period of 4.8 years a 25% lowering of the relative risk for stroke was observed in the losartan group. The results of this study could mean that the ARB losartan could confer benefits beyond reduction in blood pressure[7]. The Study on Cognition and Prognosis in the Elderly (SCOPE) randomized 4964 elderly patients with mild to moderate hypertension to the ARB candesartan or placebo, and followed them up for 4.5 years. The candersatan group showed a 10.9% relative risk reduction for stroke, myocardial infarction or death. The candesartan-based treatment reduced nonfatal stroke by 27.8% and all stroke by 23.6%. The great reduction of nonfatal and all stroke could implicate that the ARB candasartan could have some additional effects in stroke prevention besides blood pressure lowering[8].

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was a randomized, double-blind, parallel-group comparison of therapy based on valsartan or amlodipine in hypertensive patients at high cardiovascular risk. Blood pressure was reduced by both treatments

da su najjeftiniji, zaključak je da se oni trebaju prvi upotrijebiti u antihipertenzivnoj terapiji[3].

U studiji PROGRESS (Perindopril Protection Against Recurrent Stroke Study) bolesnici su bili randomizirani u skupinu koja je primala perindopril, perindopril i indapamid ili u skupinu koja je primala placebo. Studija je pokazala 25%-tno smanjenje relativnog rizika za moždani udar (ishemijskog i hemoragijskog inzulta) uz prosječno sniženje krvnog tlaka za 9/4 mm Hg[4].

Noviji klinički dokazi upućuju na to da inhibitori ACE imaju značajan učinak u prevenciji ishemijskih događaja te da zaustavljaju proces aterogeneze[13]. Pretpostavlja se da inhibitori ACE i blokatori receptora angiotenzina mogu poboljšati funkciju endotelnih stanica, usporiti progresiju ateroskleroze te smanjiti rizik od srčanog i moždanog udara[5].

Prva studija u kojoj je dokazan učinak inhibitora ACE bila je studija HOPE (Heart Outcomes Prevention Study). Studija je pokazala kako snižavanje sistoličnog krvnog tlaka za samo 3.3 mm Hg i dijastoličnog za 1.4 mm Hg uz ramipril dovodi do relativnog 32%-tnog smanjenja moždanog udara i 20%-tnog smanjenja srčanog infarkta u odnosu na skupinu koja je primala placebo. Visok postotak smanjenja cerebrovaskularnih incidenata objasnio se je mogućom nezavisnom ulogom ramiprila, uz njegov učinak na snižavanje tlaka.

Studija LIFE (Losartan Intervention For Endpoint reduction in hypertension study) nije pokazala razliku u učinku blokatora angiotenzinskih receptora losartana i beta blokatora atenolola na sniženje krvnog tlaka. Tijekom razdoblja praćenja od 4,8 godina uočeno je 25%-tno sniženje relativnog rizika za moždani udar u bolesnika koji su uzimali losartan. Ovi rezultati pokazali su kako losartan ima i druge povoljne učinke uz regulaciju hipertenzije[7].

U studiji SCOPE (The Study on Cognition and Prognosis in the Elderly) bili su randomizirani bolesnici s blagom do umjerenom hipertenzijom koji su uzimali blokator angiotenzinskih receptora kandesartan ili placebo te bili praćeni tijekom 4,5 godine. Primjena kandesartana pokazala je 27,8%-tno smanjenje moždanih udara koji nisu završili fatalno te 23,6%-tno smanjenje svih moždanih udara. Rezultati studije upućuju na to da bi kandesartan uz primarno antihipertenzivno djelovanje mogao imati i neke dodatne povoljne učinke u prevenciji moždanog udara[8].

Antagonisti kalcijevih kanala, osobito visoko lipofilni amlodipin i lacidipin, pokazali su i neka svojstva antioksidacijskog djelovanja. Istraživanja na životinjskim modelima su pokazala kako ovi lijekovi smanjuju oksidaciju čestica LDL te sprječavaju njihovo nakupljanje u stijenkama

but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (blood pressure lower by 4.0/2.1 mm Hg in amlodipine than in valsartan group after 1 month; 1.5/1.3 mm Hg after 1 year; $p<0.001$ between groups)[37].

On the other hand, CA and especially the highly lipophilic amlodipine and lacidipine may have some antioxidant properties. These drugs reduce the oxidation of LDL and its influx into the arterial wall, and reduce atherosclerotic lesions in animals. Platelet production is suppressed by amlodipine, lacidipine or nifedipine in hypertensive patients. Thus, selective CA could be potential antiatherosclerotic agents[9]. New evidence from longterm clinical trials of CA indicates that these drugs can reduce the rate of progression of atherosclerosis in hypertensive and coronary heart disease patients. In the Regression Growth Evaluation Statin Study (REGRESS), coadministration of CA, amlodipine or nifedipine with pravastatin caused a significant reduction in the appearance of new angiographic lesions[10,11]. In the Verapamil in Hypertension and Atherosclerosis Study (VHAS), verapamil was more effective than chlorthalidone in promoting regression of thicker carotid lesions in parallel with a reduction in the incidence of cardiovascular events[12]. In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), amlodipine slowed the progression of early coronary atherosclerosis in patients with coronary artery disease[13]. In a subprotocol of the Intervention as a Goal in the Hypertension Treatment (INSIGHT) study, nifedipine gastrointestinal-transport-system (GITS) significantly decreased the intima-media thickness (IMT) as compared to coamilozide (hydrochlorothiazide + amiloride)[14]. The European Lacidipine Study on Atherosclerosis (ELSA) was a randomized, double-blind trial in 2334 patients with hypertension comparing the effects of 4-year treatment with either lacidipine or atenolol on IMT in the walls of common carotids and bifurcations. Although clinical blood pressure reductions were identical with both treatments, the yearly IMT progression rate was 0.0145 mm/y in atenolol-treated and 0.0087 mm/y in lacidipine-treated patients (40% reduction). Patients with plaque progression were significantly less common, and patients with plaque regression were significantly more common in the lacidipine group. No significant difference between treatments was found in cardiovascular events, although the relative risk for stroke, major cardiovascular events and mortality showed a trend favoring lacidipine[15].

In recently published overviews of trials comparing active treatment regimens with placebo, the overview of

arterijskih krvnih žila i smanjuju aterosklerotske lezije[9]. Uz to, amlodipin, lacidipin i nifedipin suzbijaju proizvodnju trombocita u bolesnika s hipertenzijom. Rezultati novijih višegodišnjih studija upućuju na to da blokatori kalcijevih kanala smanjuju napredovanje ateroskleroze u bolesnika s hipertenzijom i koronarnom bolesti srca.

U studiju VALUE (Valsartan Antihypertensive Longterm Use Evaluation) su hipertenzivni bolesnici s visokim kardiovaskularnim rizikom randomizirani u skupinu koja je primala valsartan ili amlodipin i bili praćeni tijekom 4,2 godine. Sniženje povišenog krvnog tlaka postignuto je u objema skupinama, a učinak amlodipina bio je izraženiji, naročito na početku ispitivanja (krvni tlak je bio za 4,0/2,1 mm Hg niži u amlodipinskoj skupini u odnosu na valsartansku skupinu već nakon mjesec dana, te za 1,5/1,3 mm Hg nakon godine dana; $p<0,001$)[38].

Studija REGRESS (Regression Growth Evaluation Statin Study) pokazala je kako istodobno uzimanje amlodipina ili nifedipina u kombinaciji s pravastatinom uzrokuje značajno smanjenje novih angiografskih lezija[10,11].

Studija VHAS (Verapamil in Hypertension and Atherosclerosis Study) pokazala je bolju učinkovitost verapamila u regresiji karotidnih lezija i smanjenju incidencije cerebrovaskularnih incidenata u usporedbi s klortalidonom[12].

U studiji PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial) amlodipin je usporio progresiju početne koronarne ateroskleroze u bolesnika s koronarnom bolesti srca[13].

Studija INSIGHT (Intervention as a Goal in the Hypertension Treatment) pokazala je značajno smanjenje debljine intime i medije (*intima-media thickness*, IMT) pod utjecajem nifedipin gastrointestinalnog transportnog sustava (GITS) u usporedbi s hidroklortiazidom + amiloridom[14].

Jedna od kliničkih studija koja je uzela u obzir učinak antihipertenziva na arterijsku stijenku je studija ELSA (Europe Lacidipine Study) u kojoj je uspoređivan učinak lacidipina i atenolola. Studija je bila prospektivna, randomizirana, dvostruko slijepa, a primarni cilj je bio odrediti učinak ovih lijekova na IMT u zajedničkim karotidnim arterijma i karotidnoj bifurkaciji. Nakon četverogodišnjeg praćenja značajno smanjenje godišnje stope progresije IMT ustanovljeno je u skupini bolesnika koji su primali lacidipin, a broj bolesnika kod kojih je došlo do povećanja aterosklerotskih plakova bio je manji. Učestalost kardiovaskularnih incidenata i sniženje krvnog tlaka bili su podjednaki u objema skupinama, premda je relativni rizik za moždani udar, kardiovaskularne incidente i smrtnost bio nešto niži u skupini bolesnika koji su primali lacidipin[15].

placebo-controlled trials of ACEI (4 trials, 12124 patients mostly with coronary heart disease) revealed reductions in stroke of 30%, coronary heart disease (20%), and major cardiovascular events (21%). The overview of placebo-controlled trials of CA (2 trials, 5520 patients mostly with hypertension) showed reductions in stroke (39%) and major cardiovascular events (28%)[16]. Blood pressure lowering for primary prevention of stroke could be undertaken using a variety of therapeutic agents, but it seems that ACEI, ARB and CA could have some additional beneficial effects on stroke prevention besides blood pressure reduction[17]. Control of blood pressure must take into account adverse effects in individual patients. Generally, the lower the pressure the better, with target levels of blood pressure in the vast majority of patients and healthy individuals of below 130/70 mm Hg to minimize the occurrence of stroke and other cardiovascular complications, providing that adverse effects are acceptable to the patient[2,18].

Recently it has been shown that blood pressure reduction in the acute phase of stroke has detrimental effects[19]. Therefore, blood pressure reducing should wait until the acute phase of stroke has resolved. After that blood pressure lowering should probably be introduced slowly.

Lipid Lowering Treatment

Unlike hypertension that was long time ago recognized as a risk factor for stroke, there was considerable debate whether elevated cholesterol concentrations could be a risk factor for stroke. Previous results on the association between raised serum cholesterol levels and stroke were inconsistent. Some studies found a significant positive correlation[20,21], whereas in others no significant correlation could be found[22,23]. In the Framingham study positive correlation was found between the occurrence of stroke and elevated levels of cholesterol in men aged 50-59, if the cholesterol level exceeded 6.24 mmol/L[24].

However, recent studies have shown that lowering of cholesterol concentration definitely decreases the risk of stroke. The risk of stroke, myocardial infarction, and the need of vascular procedures were reduced by about 25% with cholesterol concentration reduction by approximately 20% in the Heart Protection Study[25]. Results of the Scandinavian Simvastatin Survival Study (4S) clearly and convincingly demonstrated the beneficial effect of cholesterol lowering on cardiovascular risk in postmyocardial infarction and angina patients. 4S provided some evidence for a beneficial effect of simvastatin on fatal plus nonfatal cerebrovascular events. The risk reduction in cerebrovascular

Pregled dosadašnjih placebom kontroliranih studija pokazuje da inhibitori ACE smanjuju moždani udar za oko 30%, koronarnu srčanu bolest za oko 20% i kardiovaskularne incidente za oko 21%. Rezultati studija inhibitora kalcijevih kanala pokazali su 39%-tno smanjenje moždanog udara i 28%-tno smanjenje kardiovaskularnih događaja[16]. Snižavanje hipertenzije u primarnoj prevenciji moždanog udara može se postići primjenom različitih antihipertenziva, ali čini se da inhibitori ACE, blokatori angiotenzinskih receptora i inhibitori kalcijevih kanala imaju i dodatan povoljni učinak u prevenciji moždanog udara[17].

Ciljne vrijednosti krvnog tlaka u većine bolesnika i zdravih pojedinaca trebale bi se održavati ispod 130/70 mm Hg, kako bi se spriječio nastanak moždanog udara i ostalih kardiovaskularnih komplikacija[2,18]. Naglo snižavanje krvnog tlaka u akutnoj fazi moždanog udara ima pogubne učinke[19], stoga antihipertenzivnu terapiju treba uvoditi polako nakon akutne faze.

Liječenje statinima

Za razliku od hipertenzije koja je odavno prepoznata kao važan rizični čimbenik za nastanak moždanog udara, često se raspravljalo oko povišenih koncentracija kolesterola kao mogućeg rizičnog čimbenika. Rezultati dosadašnjih studija o međusobnoj povezanosti povišenog serumskog kolesterola i moždanog udara nisu bili dosljedni. Neki od njih pokazali su značajnu pozitivnu korelaciju[20,21], dok ostale studije nisu potvrdile navedene rezultate[22,23].

U Framinghamskoj studiji pronađena je pozitivna korelacija između nastanka moždanog udara i povišenih vrijednosti kolesterola u muškaraca u dobi između 50 i 59 godina, s koncentracijom kolesterola višom od 6,24 mmol/L[24].

Rezultati novijih studija pokazali su kako snižavanje koncentracije kolesterola ipak smanjuje rizik od moždanog udara.

Rezultati ispitivanja Scandinavian Simvastatin Survival Study (4S) jasno su potvrdili povoljan učinak snižavanja koncentracije kolesterola na kardiovaskularni rizik nakon preboljelog srčanog infarkta te u bolesnika s pektoralnom anginom. Studija 4S pokazala je 28%-tno smanjenje rizika za cerebrovaskularne događaje (moždani udar i TIA) uz 24%-tno smanjenje rizika za moždani udar[26,27].

Studija CARE (Cholesterol And Recurrent Events) u kojoj su randomizirani bolesnici uzimali pravastatin ili placebo pokazala je 32%-tno smanjenje svih moždanih udara i 27%-tno smanjenje moždanog udara ili TIA u onih ispitanika koji su primali pravastatin[28].

events (stroke and TIA) was 28%. The risk reduction in stroke was 24%[26,27]. Two studies of pravastatin therapy were designed with stroke as a prespecified endpoint. The Cholesterol And Recurrent Events (CARE) study involved 4159 patients. Patients were randomized to receive pravastatin 40 mg once daily or placebo. Compared with placebo, pravastatin therapy resulted in a 32% reduction in all-cause stroke and 27% reduction in stroke or TIA (28). Longterm Intervention with Pravastatin in Ischemic Disease (LIPID) trial compared the effects of pravastatin 40 mg once daily on mortality due to coronary heart disease (the primary end point) with the effects of placebo among 9014 patients with a history of myocardial infarction or unstable angina. The risk reduction for total stroke (fatal and non-fatal) in the LIPID trial was 19% with pravastatin compared with placebo, but pravastatin had no effect on hemorrhagic stroke[29]. In the Aggressive *versus* conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP) trial, carotid IMT measured by quantitative B-mode ultrasound decreased (-0.031 mm) in the atorvastatin group (80 mg daily) after 2 years, whereas in the simvastatin group (40 mg daily) it increased (0.036 mm) in 325 patients with familial hypercholesterolemia[30]. The Collaborative Atorvastatin Diabetes Study (CARDS) was a multicenter randomized placebo-controlled trial testing the efficacy of atorvastatin in primary prevention of cardiovascular disease in type 2 diabetes. Assessed separately, the acute coronary disease events were reduced by 36%, coronary revascularizations by 31%, and the rate of stroke by 48%. Atorvastatin reduced death rate by 27%. Results of the study showed atorvastatin 10 mg daily to be safe and efficacious in reducing the risk of first cardiovascular disease events including stroke in patients with type 2 diabetes without high LDL-cholesterol[38].

In the Heart Protection Study allocation to 40 mg simvastatin daily significantly reduced all-cause mortality chiefly due to the definite 17% proportional reduction in death rate from vascular causes in 20,536 high-risk individuals. In the simvastatin group there was a significant 25% proportional reduction in the incidence of first stroke. This was mainly due to a definite 30% proportional reduction in the incidence of strokes attributed to ischemic stroke, whereas there was no apparent difference in hemorrhagic stroke. Also, there was a significant reduction in the number of subjects who had at least one episode of transient cerebral ischemia[25].

Although most of recent studies showed beneficial effect of statins in reducing the risk of stroke, the Antihy-

Placebom kontrolirana studija LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) ispitivala je učinak pravastatina na smrtnost od koronarne srčane bolesti u bolesnika s preboljelim infarktom miokarda i nestabilnom pektoralnom anginom. Rezultati studije su pokazali 19%-tno smanjenje rizika za moždani udar u bolesnika koji su primali pravastatin[29].

U studiji ASAP (Aggressive *versus* conventional lipid lowering on Atherosclerosis Progression in familial hypercholesterolemia) uspoređivao se je učinak pojedinih statina. Prospektivno praćenje IMT u karotidnim arterijama tijekom 2 godine pokazalo je da se kod ispitanika koji su uzimali atorvastatin IMT značajno smanjila, za razliku od onih iz skupine koja je primala simvastatin[30].

Studija CARDS (Collaborative Atorvastatin Diabetes Study) ispitivala je učinak atorvastatina (10 mg/dan) u primarnoj prevenciji glavnih kardiovaskularnih događaja u oboljelih od šećerne bolesti tipa 2 koji nisu imali visoku koncentraciju LDL kolesterola u serumu. Bolesnici su randomizirani u skupinu koja je uzimala atorvastatin ili u skupinu koja je dobivala placebo, a praćeni su tijekom 3,9 godina. Rezultati studije pokazali su 36%-tno smanjenje akutne koronarne bolesti srca i 48%-tno smanjenje moždanog udara. Stopa smrtnosti smanjena je za 27% u skupini na atorvastatinu, ukazujući na učinkovitost primjene atorvastatina u primarnoj prevenciji kardiovaskularnih bolesti i moždanog udara u onih bolesnika sa šećernom bolešću tipa 2 koji nemaju povišen LDL kolesterol[39].

Studija HPS (Heart Protection Study) uključila je u ispitivanje bolesnike kod kojih je bilo malo izravnih dokaza o potencijalnoj koristi od uzimanja statina (dijabetičari, starije osobe, osoobe s normalnim vrijednostima kolesterola). Bolesnici su dobivali 40 mg simvastatina ili placebo, a praćeni su prosječno 5 godina. U skupini koja je primala simvastatin zabilježeno je smanjenje ukupne smrtnosti, većinom zbog definitivnog 17%-tnog proporcionalnog smanjenja stope smrtnosti vaskularne etiologije. U simvastatinskoj skupini zabilježeno je i značajno 25%-tno proporcionalno smanjenje incidencije moždanog udara te broja ispitanika koji su imali bar jednu epizodu TIA[25].

U studiji ALLHAT-LLT (Antihypertensive and Li-pid-Lowering Treatment to Prevent Heart Attack), u koju su bili uključeni stariji bolesnici s dobro kontroliranom hipertenzijom i umjereno povišenim LDL-C, pravastatin nije pokazao značajno smanjenje ukupne smrtnosti niti koronarne bolesti srca[31].

Nedavno objavljena meta-analiza koja je uključila 164 kratkoročne, randomizirane placebom kontrolirane studije o utjecaju statina na snižavanje LDL kolesterola, 58 ran-

pertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in 10,355 older participants with well-controlled hypertension and moderately elevated LDL-C receiving either pravastatin 40 mg daily or usual care revealed a similar all-cause mortality for the 2 groups. Pravastatin failed to reduce either all-cause mortality or coronary heart disease significantly when compared with usual care[31].

In a recently published meta-analysis of 164 short-term randomized placebo controlled trials of six statins and LDL cholesterol reduction; 58 randomized trials of cholesterol lowering by any means and ischemic heart disease events; and nine cohort studies and the same 58 trials on stroke, it is concluded that statins can lower low density lipoprotein-cholesterol (LDL cholesterol) concentration by an average of 1.8 mmol/L, which reduces the risk of ischemic heart disease events by about 60% and of stroke by only 17%. In people with existing vascular disease the reduction of stroke is 36%[32].

In conclusion, it seems that there is a statistical link between elevated low-density lipoprotein cholesterol or decreased high-density lipoprotein cholesterol and ischemic stroke, and a reduction in vascular risk with statins in randomized trials in patients with coronary heart disease. Also, there is evidence for a decreased plaque progression under statins; and pooled analyses of primary and secondary prevention trials showing that reduction of total serum cholesterol reduces the incidence of stroke, especially with the highest rate of cholesterol reduction, and in patients with the highest risk of stroke[33].

Elevated apolipoprotein B (apoB) is known to be an important risk factor for coronary heart disease, and dysregulation of the metabolism of apoB-containing lipoproteins is involved in the progression of atherosclerosis. Statins reduce circulating concentrations of atherogenic apoB-containing lipoproteins by decreasing the production of VLDL in the liver[34].

It seems that besides the cholesterol lowering potential statins may improve endothelial-dependent flow-mediated vasodilatation by increasing the bioavailability of nitric oxide. They may stabilize the plaque by modulating the inflammatory response within the vessel wall. They also may decrease clot formation by decreasing the adherence of platelets to the ruptured plaque and by acting on the extrinsic coagulation cascade pathway[35].

Statins possess anti-inflammatory properties, as evidenced by their ability to reduce the accumulation of inflammatory cells in atherosclerotic plaques; they inhibit vascular smooth muscle cell proliferation (a key event in

domiziranih studija o utjecaju snižavanja kolesterola na ishemijsku bolest srca i moždani udar i 9 kohortnih studija pokazala je kako statini mogu smanjiti koncentraciju čestica LDL za 1,8 mmol/L, što smanjuje rizik od ishemijske bolesti srca za oko 60% i moždanog udara za oko 17%. U bolesnika s već postojećom vaskularom bolesti smanjenje moždanog udara iznosilo je 36%[32].

Čini se da postoji statistička povezanost između povišenog LDL i sniženog HDL kolesterola i ishemijskog moždanog udara te smanjenja vaskularnog rizika uz primjenu statina u bolesnika s koronarnom bolesti srca. Dokazi upućuju na to da statini smanjuju napredovanje plaka, a sniženje ukupnog kolesterola u serumu smanjuje incidenciju moždanog udara[33].

Povišen apolipoprotein B (apoB) je važan čimbenik rizika za koronarnu bolest srca, a poremećena regulacija metabolizma lipoproteina koji sadržavaju apoB povezana je s napredovanjem ateroskleroze. Statini smanjuju koncentraciju cirkulirajućeg aterogenog apoB-lipoproteina smanjujući proizvodnju VLDL u jetri[34]. Pretpostavlja se da uza snižavanje koncentracije kolesterola statini mogu poboljšati vazodilataciju povećavajući bioraspoloživost nitričnog oksida te da mogu stabilizirati plak smanjujući upalni odgovor u stijenci krvne žile. Nadalje, statini mogu umanjiti stvaranje krvnog ugruška smanjujući adheziju trombocita na rupturiranom plaku djelujući preko vanjskog puta aktivacije koagulacije[35]. Statini posjeduju protuupalna svojstva te smanjuju nakupljanje upalnih stanica u aterogenom plaku, suzbijaju funkciju trombocita i poboljšavaju vaskularnu funkciju endotela povećavajući koncentraciju nitričnog oksida[36].

Zaključak

Liječenje hipertenzije i hiperkolesterolemije ima važnu ulogu u primarnoj i sekundarnoj prevenciji moždanog udara. Rezultati velikih randomiziranih kliničkih studija pouzdano su pokazali da je sniženje krvnog tlaka i povišenog kolesterola povezano sa značajnim smanjenjem rizika od nastanka moždanog udara.

Inhibitori ACE i blokatori angiotenzinskih receptora mogu poboljšati funkciju endotela i usporiti napredovanje ateroskleroze. Antagonisti kalcijevih kanala koji su visoko lipofilni imaju i neka antioksidacijska svojstva. Rezultati na životinjskim modelima pokazali su kako statini smanjuju oksidaciju i ulaz čestica LDL u stanice arterijske stijenke. Amlodipin, lacidipin i nifedipin suzbijaju stvaranje trombocita u bolesnika koji boluju od hipertenzije, te maju potencijalna antiaterosklerotska svojstva.

atherogenesis), they inhibit platelet function, and they improve vascular endothelial function, largely through augmentation of nitric oxide generation[36].

Conclusion

Nowadays there is no doubt that treatment of hypertension and hypercholesterolemia has significant role in primary and secondary prevention of stroke. Data from large randomized clinical trials published recently convincingly show that lowering of blood pressure and reduction of elevated cholesterol are associated with a significant decrease in the risk of stroke. Furthermore, it seems that the use of ACEI, ARB, CA and statins could provide some additional beneficial effects besides blood pressure and cholesterol lowering[39].

ACEI and ARB could improve endothelial function, cardiac and vascular remodeling, and retard the anatomic progression of atherosclerosis. CA, especially the highly lipophilic ones, may have some antioxidant properties. They reduce the oxidation of LDL and its influx into the arterial wall, thus reducing atherosclerotic lesions in animals. Amlodipine, lacidipine or nifedipine suppress platelet production in hypertensive patients. Thus, selective CA could be potential antiatherosclerotic agents.

Besides cholesterol reduction, statins could have other beneficial effects such as improvement of endothelial-dependent flow-mediated vasodilatation, stabilizing atherosclerotic plaque, modulating the inflammatory response, decreasing clot formation, and decreasing the adherence of platelets to the ruptured plaque. Other antiatherosclerotic properties of statins include reducing of accumulation of inflammatory cells in atherosclerotic plaques, inhibiting vascular smooth muscle cell proliferation, inhibiting platelet function, and improving of vascular endothelial function.

Taking into account all these data it could be supposed that a wider use of these drug classes could significantly improve our ability to prevent all vascular diseases and stroke in particular. The data from large randomized clinical trials shed bright light for stroke prevention in the forthcoming future.

Uza snižavanje koncentracije kolesterola statini pospješuju vazodilataciju, stabiliziraju plak, utječu na upalni odgovor u endotelnim stanicama, smanjuju stvaranje krvnih ugrušaka i smanjuju adheziju trombocita na rupturiranom plaku.

Ostala antiaterosklerotska svojstva statina uključuju smanjenje nakupljanja upalnih stanica u plaku, inhibiciju proliferacije glatkomišićnih stanica krvne stijenke, inhibiciju funkcije trombocita i poboljšanje vaskularne funkcije endotelnih stanica. Na temelju navedenog možemo pretpostaviti da bi šira primjena novijih antihipertenziva i statina mogla značajno poboljšati prevenciju svih cerebrovaskularnih bolesti, a poglavito moždanog udara[37].

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MICROVASCULAR END ENDOVASCULAR MANAGEMENT OF CEREBRAL ANEURYSMS

MIKROVASKULARANE I ENDOVASKULARNE METODE LIJEČENJA MOŽDANIH ANEURIZMATSKIH TVORBA

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The management of cerebral aneurysms is still a subject of controversy in spite of recent advances in microneurosurgery and interventional neuroradiology. This advancement has brought a new aspect in the treatment of aneurysms.

After an aneurysm is demonstrated arteriographically, the neurosurgeon must decide how and when to obliterate the aneurysm. In the earlier days of aneurysm treatment, surgery was delayed until the second or third week after the initial hemorrhage to avoid difficulty related to swollen brain during surgery. Although this lowered surgical morbidity and mortality rates, management results were not always good because of a high incidence of rebleeding and difficulty in managing vasospasm.

Currently there are two main topics in this field which are correlated with technical development:

1. advances in microsurgical techniques regarding the management of cerebral aneurysms, and
2. advances in endovascular techniques regarding the management of cerebral aneurysms.

The most desirable treatment for aneurysmal subarachnoid hemorrhage (SAH) is early surgery to clip the aneurysm and prevent further bleeding. Microsurgical treatment for aneurysms involves a surgical procedure to expose the aneurysm by slipping under and around the brain using delicate instruments and high powered magnification. The goal of surgical treatment is usually to place a clip across the neck of the aneurysm to exclude the aneurysm from the circulation. With the aneurysm appropriately clipped, the risk of rehemorrhage is avoided.

Intracranial clipping of a ruptured aneurysm is curative and can usually be done with low morbidity. After an aneurysm has ruptured, the timing of surgery is important for patient outcome. The past practice was to wait for approximately 2 weeks after the SAH before surgery, based on the premise that the patient was a better surgical candidate once cerebral edema had subsided and he/she was

Liječenje cerebralnih aneurizmatskih tvorba predstavlja velik izazov te s njim u vezi još uvijek postoje brojna proturječja naznačene napretkom kako mikroneurokirurških tako i interventnih neuroradioloških metoda, koji navedenim metodama liječenja daje novu ulogu i značenje.

Nakon dijagnosticiranja aneurizmatske tvorbe neurokirurg treba odlučiti kako i kada obliterirati aneurizmatsku tvorbu. U ranom razdoblju razvoja neurokirurgije operacijski zahvat odgađao se je do kraja drugog ili trećeg tjedna, s namjerom da se izbjegnu tehničke poteškoće pri prepariranju aneurzimatskog kompleksa vezane uz postojanje edema moždanog parenhima. Ovakav način operacijskog liječenja, tj. odgođena operacija, smanjuje stope pobola i smrtnosti zahvata, međutim, ukupni rezultati liječenja nisu uvijek bolji zbog visoke učestalosti ponovnog krvarenja i patofizioloških procesa uzrokovanih vazospazmom.

Napretkom tehnologije mijenja se dijelom i strategija u liječenju cerebralnih aneurizma i to s obzirom na:

1. razvoj mikroneurokirurške tehnike u liječenju cerebralnih aneurizma;
2. razvoj novih endovaskularnih tehnika u liječenju cerebralnih aneurizma.

Najprimjereniji način liječenja rupturiranih cerebralnih aneurizmatskih tvorba je rana neurokirurška operacija s ciljem okludiranja vrata aneurizme te njenim isključenjem iz cirkulacije i na taj način sprječavanjem ponovne rupture.

Postupak prepariranja aneurizmatskog kompleksa i prikazivanja vrata i tijela aneurizme izvodi se upotrebom operacijskog mikroskopa (magnifikacija i iluminacija) te specijalnih mikroneurokirurških instrumenata. Cilj neurokirurškog liječenja je postavljanje metalnog klipića na vrat aneurizme. Na taj način aneurizma se isključuje iz cirkulacije, te ako je aneurizma primjereno klipana rizik od ponovne rupture je sveden na minimum.

Ovakav način liječenja vrlo je djelotvoran i praćen je niskom stopom pobola i smrtnosti.

medically stabilized. However, a delay of 2 weeks spans the peak times for two of the most dangerous complications of SAH, rebleeding and vasopasm. As the result of several multicenter studies to determine the optimum time of surgery, there has been a definite trend toward surgery within 48 to 72 hours of SAH for patients in Hunt and Hess clinical grades I and II and, in some situations, grade III. Patients in grades IV and V are treated medically for potential future surgery at a later date. Surgery is usually not performed at all in the presence of coma or severe neurologic deficits due to the low recovery and high mortality rate.

The current standard of surgical practice calls for microsurgical dissection and clipping of the aneurysmal neck whenever possible. Surgical morbidity is determined by numerous factors, including the location, size, and configuration of the aneurysm; the medical and neurologic condition of the patient; and the coincidence of other complications of SAH. Decisions about the timing of surgery, the surgical approach, and specific technical adjuncts to surgery must be based on the individual clinical setting.

Special strategies are mandatory for optimal surgical management of aneurysms of special location, size and form. Appropriate selection of surgical approaches is of cardinal importance in the management of aneurysms, especially those with special locations and size. This is to be done in accordance with the angioanatomical findings of aneurysms.

For example: selective extradural anterior clinoidectomy (SEAC) covers special aneurysms of the anterior circulation, especially of paraclinoid aneurysms along with aneurysms of the upper portion of the basilar artery with aneurysmal neck located above the level of the posterior clinoid process.

Subtemporal approach with anterior petrosectomy covers aneurysms of the basilar artery with aneurysmal neck below the level of the posterior clinoid process.

The lateral suboccipial craniotomy combined with partial occipital condilectomy solves the problems of special aneurysm arising from the vertebral artery.

The supracerebellar transtentorial approach enables us to reach distal parts of the posterior cerebral artery aneurysms.

Microsurgical techniques have been around for many years and are constantly advancing. Long-term follow-up of patients after microsurgical clipping is available and shows an excellent success rate in preventing rebleeding.

During the past decade, endovascular methods have been developed to treat intracranial aneurysms. Inter-

Vrijeme operacijskog liječenja nakon rupture aneurizme jedan je od važnijih čimbenika koji utječu na ishod tijeka bolesti.

U ranijoj fazi razvoja neurokirurgije više se je primjenjivao odgođeni operacijski zahvat, tj. kasna operacija (2 do 3 tjedna nakon rupture), što se je zasnivalo na premisi da je operaciju tehnički primjerenije izvoditi nakon stabiliziranja općeg stanja bolesnika i regresije edema moždanog parenhima. Međutim, odgađanjem operacije povećava se incidencija dviju najčešćih komplikacija subarahnoidne hemoragije: ponovne rupture aneurizmatske tvorbe i progresije vazospazma. Nakon niza ispitivanja iz multicentričnih studija kojima je bio cilj utvrditi optimalno vrijeme provođenja operacije možemo reći kako danas vrijedi pravilo da bolesnike s kliničkim stanjem prema Huntovoj i Hessovoj ljestvici I. i II., a u određenim uvjetima i III. operiramo hitnom operacijom, tj. unutar 48 do 72 sata od rupture aneurizme.

Bolesnike s kliničkim stanjem IV. i V. stupnja operiramo odgođenom operacijom ako dođe do stabilizacije stanja.

Bolesnike u stanju moždane kome nije indicirano operacijski liječiti zbog izrazito visoke smrtnosti. Kliničko stanje bolesnika prije operacije najvažniji je prognostički čimbenik u liječenju ovih tvorba.

Kirurški pobol i smrtnost uvjetovani su nizom čimbenika poput: lokalizacije, veličine i oblika aneurizmatske tvorbe; općeg i neurološkog statusa bolesnika; razvoja brojnih komplikacija subarahnoidnog krvarenja.

Odabir vrste neurokirurškog zahvata i specifičnih tehnika posebno je važan u slučajevima postojanja aneurizma specifične lokalizacije, veličine i oblika.

Odgovarajuća cerebralna angiografija koja nam otkriva detalje navedenih morfoloških značajka aneurizmatskih tvorba od najveće je važnosti pri planiranju operacijskog zahvata.

Niže su opisani neki od specijalnih operacijskih pristupa na cerebralne aneurizme.

Selektivna ekstraduralna prednja klinoidektomija (SEAC, *selective extradural anterior clinoidectomy*), kojom možemo pristupiti na paraklinoidno lokalizirane aneurizme i aneurizme račvišta bazilarne arterije kojima je vrat aneurizme lokaliziran iznad razine stražnjeg klinoida.

Subtemporalni pristup uz prednju petrosektomiju omogućava nam pristup na aneurizme račvišta bazilarne arterije kojima je vrat lokaliziran ispod razine stražnjeg klinoida.

Lateralni subokcipitalni pristup uz parcijalnu okcipitalnu kondilektomiju omogućava nam pristup na aneurizme lokalizirane na vertebralnoj arteriji.

ventional neuroradiology, a new subspecialty in radiology, has created new options for the management of cerebral aneurysms. This metod has become widely accepted as an alternative to direct surgery.

Intravascular detachable coils therapy involves use of superselective catheters that can enter the vessels previously inaccessible with normal catheters. Generally, patients selected for this option are poor surgical candidates. Such patients have aneurysms that are anatomically unclippable or that are located in accessible areas. A catheter is inserted into the patient's peripheral artery and navigated by using an angiogram as a "road map" to the area where the aneurysm is located. Once found, the aneurysm is then filled from the inside with tiny platinum coils. The coils react with the surrounding blood causing it to clot thereby obliterating the aneurysm.

Coils embolization is a relatively safe treatment with low incidence of periprocedural morbidity, and has been successful in preventing acute subsequent bleeding, whereas follow-up results are less satisfactory in cases involving incompletely obliterated lesions. Complications of intravascular coils therapy also include rupture of the aneurysm, hemorrhage, cerebral ischemia, or cerebral infarction leading to a stroke syndrome. The parent vessel that supplies blood to the area of the aneurysm may also be occluded using this method. The risk of rebleeding after treatment with detachable coils may be similar to that for incompletely clipped aneurysms.

Endovascular treatment for cerebral aneurysms is a promising new technique. However, its long-term effectiveness is not yet known and some patients may require close follow-up or possibly additional treatments.

Published reports of early clinical and angiographic results have been promising, but long-term efficacy of this method remains to be determined. Some analysis evaluated the anatomical evolution of the neck remnant in the aneurysms treated with coils. About 25% of aneurysms with neck remnant exhibited progressive thrombosis, 26% remained unchanged, and 49% displayed recanalization on follow-up angiography. The size of aneurysm neck correlates well with the initial morphological results of the endovascular treatment. In cases of wide-necked aneurysm, neointimal formation across the aneurysm neck was rarely completed, furthermore, looser packing with coils may prevent neointimal and neoendothelial proliferation across the neck of aneurysm.

Both the microsurgical and endovascular therapies have advantages and disadvantages. A treatment that is appropriate for one patient may not be appropriate for another. Treatment plan is carefully individualized to each patient.

Supracerebeleranim transtentorijalnim pristupom moguće je operacijski liječiti aneurizme distalnog dijela stražnje cerebralne arterije.

Mikroneurokirurška tehnika je već duže vrijeme u upotrebi, no i dalje napreduje, prvenstveno zahvaljujući razvoju boljih optičkih pomagala – mikroskopa i mikroneurokirurškog instrumentarija.

Danas imamo brojne statističke serije praćenja uspješnosti neurokirurškog liječenja cerebralnih aneurizma, koje ukazuje na vrlo dobre, za pojedine lokalizacije aneurizma i odlične rezultate u liječenju ovih tvorba.

Sa druge strane, u posljednjem desetljeću razvijaju se i endovaskularne metode u liječenju intrakranijskih aneurizmatskih tvorba. Tako se je razvila i intervencijska neuroradiologija, nova radiološka subspecijalnost koja nam pruža nove mogućnosti za liječenje cerebralnih aneurizma. Ova metoda nailazi na sve širu primjenu i kao takva postaje pravom alternativom kirurškoj terapiji.

Temelj endovaskularne terapije je upotreba odvojivih zavojnica (*coils*), najčešće platinastih, koje se supraselektivnim kateterima uvode endovaskularnim putem u aneurizmu. Aneurizma se potom puni zavojnicama radi obliteracije njenog fundusa i time isključenja iz cirkulacije.

U početku su se ovom vrstom terapije liječili samo bolesnici koji nisu bili prikladni za operacijsko liječenje: bolesnici lošeg kliničkog stanja i bolesnici s aneurizmama težih lokalizacija.

Embolizacija aneurizma zavojnicama relativno je sigurna metoda s niskim periproceduralnim morbiditetom i mortalitetom. Međutim, rezultati sprječavanja ponovne rupture (*rerupture*) nisu zadovoljavajući u slučajevima nepotpune obliteracije aneurizme zavojnicama. Komplilkacije ovakvih zahvata su: ruptura aneurizme, cerebralna ishemija, ponekad razvoj cerebralne infrakcije.

Glavna krvna žila na kojoj je razvijena aneurizma može se okludirati zavojnicama, ako one "iziđu" iz aneurizme, gdje se primarno postavljaju.

Usprkos nedostacima endovaskularne metode imaju svoju ulogu u liječenju cerebralnih aneurizma, a zahvaljujući tehnološkom napretku predstavljaju obećavajuću terapijsku opciju.

U ovom trenutku još ne postoje dugoročni statistički rezultati liječenja bolesnika ovom metodom, međutim, u tijeku je niz velikih serija kojima je cilj usporedba kirurškog i endovaskularnog liječenja aneurizma.

Zasad postoje analize morfoloških promjena aneurizme u bolesnika s nepotpunom obliteracijom aneurizme upotrebom zavojnica.

Whether to obliterate an aneurysm surgically through a craniotomy and clipping or to use endovascular methods is a decision made by the neurosurgeon and endovascular radiologist as a team, based on which approach best suits each patient's aneurysm. The general consensus today is that treatment depends on the age and clinical status of the patient, and on the location of the aneurysm. Younger patients tend to undergo surgical clipping because coiling has a high recurrence rate. Posterior fossae aneurysms (especially the basilar artery tip) tend to be treated with the coil procedure. In most major aneurysm centers, most cases are still obliterated by surgical clipping, but coiling is being ever more frequently used. Some complex aneurysms may require a combination of both major treatment techniques or even other types of procedures.

Given the complexity of evaluation, treatment and management of aneurysmal SAH, a team approach to the problem has proved useful. Neurosurgeons, interventional neuroradiologists, neurologists and anesthesiologists work together on specific management issues to select and implement treatment to optimize outcome.

U oko 25% slučajeva s "ostatnim vratom" aneurizme dolazi do daljnje obliteracije aneurizme uvjetovane trombozom, u 26% slučajeva ne dolazi do promjena, dok u čak 49% slučajeva dolazi do rekanalizacije na kontrolnim angiografijama.

Također je poznato da veličina vrata aneurizme izravno korelira s rezultatima liječenja aneurizma endovaskularnim metodama.

Velik vrat je u većini slučajeva neporemostiva prepreka neointimalnoj i neoendotelijskoj proliferaciji i obliteraciji aneurizme.

Naposlijetku možemo reći da kako neurokirurške tako i endovaskularne metode liječenja cerebralnih aneurizma imaju svoje prednosti i nedostatke.

Terapijski plan treba pažljivo procijenjivati u svakom pojedinačnom slučaju posebno. Odluka o tome u ovlasti je tima koji čine neurokirurg, neuroradiolog, neurolog i anesteziolog. Danas je uvriježeno mišljenje da se odluka donosi individualno za svakog bolesnika, ovisno o njegovom kliničkom statusu i lokalizaciji aneurizme.

Mlađi bolesnici prikladniji su za kirurško liječenje zbog visoke učestalosti ponovnog krvarenja kod neprimjereno obliteriranih aneurizma liječenih endovaskularno. Aneurizme težih lokalizacija, poput aneurizma račvišta bazilarne arterije češće se liječe upotrebom endovaskularnih tehnika zbog visokog periproceduralnog pobola i smrtnosti pri kirurškom liječenju aneurizma ove lokalizacije.

Neke kompleksne aneurizme moguće je liječiti i kombinacijom obiju tehnika: neurokirurške i endovaskularne obliteracijske tehnike.

STROKE PREVENTION BY CAROTID ENDARTERECTOMY: CURRENT STATE AND FUTURE PERSPECTIVE

PREVENCIJA MOŽDANOG UDARA KAROTIDNOM ENDARTEREKTOMIJOM: SADAŠNJE STANJE I PERSPEKTIVA

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Summary

Own experience and results obtained with carotid endarterectomy (CEA) from January 1970 till August 31, 2004 are presented. A total of 2342 CEA procedures were performed in 2223 patients (bilateral operation in 5.4% of patients), 692 (31.1%) women and 1531 (68.9%) men, mean age 65.8±9.3 (range 38-98) years. Most operations were performed in general anesthesia, and from October 14, 2002 90% of the procedures were done in locoregional anesthesia. The techniques of open, conventional and eversion CEA (from 1985) were employed. The best results in the perioperative period to postoperative day 30 were recorded on operating on asymptomatic patients (341 CEA; 14.5% of total). There was no lethal outcome, and the rate of stroke was 0.3%. A total of 2001 symptomatic stenoses were operated on, i.e. 1098 after transient ischemic attack (TIA), 894 after completed stroke, and 9 on stroke in evolution, yielding the respective rates of stroke and mortality of 1%, 3.1% and 55.5%. The results obtained in asymptomatic and symptomatic stenoses operated on (except those in progressive stroke) are very satisfactory and comaparable with the best in the world. Due to the disastrous results of the procedure performed on stroke in evolution, we believe that, in our circumstances, this indication is not justifiable and that these patients are better treated at neurologic intensive care units. In spite of the observed trend and encouraging results of urgent carotid surgery, we have no such experience of our own. The current indications for CEA and controversies about indications in asymptomatic patients are discussed, with special reference to recently (2004) published results of the ACST and ACSRS studies. It is quite clear that categorization of patients candidates for CEA, which is based solely on the degree of stenosis and presence or absence of neurologic symptoms is not precise enough for assessment of the real individual risk of stroke. As CEA has been definitely scientifically verified as an efficient method of surgical treatment for carotid occlusive disease and for stroke prevention, all the possibilities it offers should be maximally used. Unfortunately, in Croatia only 15% of the real needs for CEA are

Sažetak

Prikazana su iskustva i rezultati s karotidnom endarterektomijom (KEA) u razdoblju od siječnja 1970. do 31. kolovoza 2004. godine. Ukupno su izvedena 2342 postupka KEA u 2223 bolesnika (5,4% obostranih operacija), od čega 692 (31,1%) žene i 1531 (68,9%) muškarac. Srednja dob operiranih bila je 65,8±9,3, raspon 38-98 godina. Većina operacija učinjena je u općoj anesteziji, a od 14. listopada 2002. godine 90% u lokoregionalnoj anesteziji. Primijenjene su tehnike otvorene, konvencionalne i everzijske KEA (od 1985. godine). Najbolje rezultate u perioperacijskom razdoblju do 30 dana nakon operacije postigli smo operirajući asimptomatske bolesnike (341 KEA, 14,5% od ukupnog broja). Nismo imali smrtnog ishoda, a stopa moždanog udara bila je 0,3%. Ukupno je operirana 2001 simptomatska stenoza, tj. 1098 nakon prolaznog ishemijskog napadaja (TIA), 894 nakon završenog moždanog udara, te 9 u moždanom udaru u evoluciji sa stopama moždanog udara i smrtnosti od 1% 3,1% odnosno 55,5%. Rezultati kod operiranih asimptomatskih i simptomatskih stenoza (osim onih u progresivnom moždanom udaru) su vrlo zadovoljavajući i usporedivi s najboljima u svijetu. Zbog katastrofalnih rezultata operacija u moždanom udaru u evoluciji smatramo kako u našim okolnostima indikacije nisu opravdane, te da je bolje bolesnike liječiti u jedinicama intenzivne neurološke skrbi. Usprkos zapaženom trendu i ohrabrujućim rezultatima hitne karotidne kirurgije mi nemamo vlastitih iskustava. Raspravlja se o suvremenim indikacijama za KEA, proturječjima u indiciranju kod asimptomatskih bolesnika, s osvrtom na nedavno objavljene rezultate (2004.) studija ACST i ACSRS. Očito je kako kategorizacija bolesnika kandidata za KEA, koja se temelji samo na stupnju stenoze i prisutnosti/odsutnosti neuroloških simptoma, nije dovoljno precizna za procjenu stvarnog pojedinačnog rizika od moždanog udara. Kako je KEA nedvojbeno znanstveno dokazana kao učinkovita metoda kirurškog liječenja okluzivne karotidne bolesti i prevencije moždanog udara, treba maksimalno iskoristiti sve njene mogućnosti. Nažalost, u Hrvatskoj se operira samo 15% od stvarnih potreba za KEA. Budućnost endovaskularnog pristupa ne bi se trebala zasnivati

managed by this method. The future developments of endovascular approach should not be based on competition but on complementarity, however, provided the same validation as for CEA.

Key words: *carotid endarterectomy, stroke prevention, carotid occlusive disease, atherosclerosis*

Introduction

Atherosclerosis accounts for about 90% of extracranial cerebral artery pathology, predominantly localized at carotid bifurcation (75% of caes), with earliest and most common internal carotid artery involvement. The shape (the geometrical risk factor for atherogenesis!) and hemodynamics of carotid bifurcation are responsible for the most common seat of atherosclerosis in precerebral arteries[1].

Besides cardiac arrhythmias, carotid occlusive disease (COD) is an immediate cause of ischemic stroke as well as a marker of coronary and peripheral atherosclerotic obliterative disease. (Peripheral atherosclerotic obliterative disease is present in 35% of patients with COD, whereas 40% of candidates for carotid endarterectomy have severe coronary disease.)

According to the WHO[2], stroke is the second leading cause of mortality woldwide. The age adjusted prevalence of stroke among individuals aged ³65 is 46-72 *per* 1000[3]. Several studies have shown that ischemic stroke is a predominant subtype that accounts for 67%-81% of all strokes, with a one-month mortality rate of 16%[3]. In 1990, stroke was the sixth most common cause of disability and disablement, and is estimated to be the fourth one by the year 2020[4]. The cost of treatment *per* patient following ischemic stroke during life is 60,000-230,000 USD[5]. In Croatia in 2000, stroke (unspecified as hemorrhage or ischemic infarction) was the first of ten leading causes of death with 6,614 (13.2%) deaths and mortality rate of 151/100,000 population[6]. Screening for the three direct causes of stroke, i.e. hypertension, cardiac arrhythmias and COD along with primary prevention is the most important part of the strategy to reduce stroke burden[7].

Carotid endarterectomy (CEA) and novel endovascular carotid interventions (carotid balloon angioplasty (CBA) with or without stenting, carotid artery stenting (CAS)) primarily imply a preventive concept in the overall approach in the management of stroke, and have found place in secondary prevention. Their aim is to prevent the occurrence of acute and recurrence of even more severe ischemic stroke as well as the associated disability and death, and to prevent transient cerebral dysfunction. A rational requirement is that the results of treatment should be

na kompeticiji, nego na komplementarnosti, ali uz istu znanstvenu valorizaciju kao i za KEA.

Ključne riječi: *karotidna endarterektomija, prevencija moždanog udara, karotidna okluzivna bolest, ateroskleroza*

Uvod

Ateroskleroza čini oko 90% patologije ekstrakranijskih cerebralnih arterija i do u 75% slučajeva prevladava lokalizacija na karotidnoj bifurkaciji zahvaćajući najranije i najviše unutarnju karotidnu arteriju. Oblik (geometrijski čimbenik rizika aterogeneze!) i hemodinamika karotidne bifurkacije odgovorni su za najčešće sijelo ateroskleroze na precerebralnim arterijama[1].

Karotidna okluzivna bolest (*carotid occlusive disease*, COD) je uza srčane aritmije najčešći izravan uzrok ishemijskog moždanog udara, ali i biljeg koronarne i periferne aterosklerotske obliterativne bolesti. (Perifernu aterosklerotsku obliterativnu bolest ima oko 35% bolesnika s COD, a oko 40% kandidata za karotidnu endarterektomiju ima tešku koronarnu bolest.)

Prema podacima SZO[2], moždani udar je drugi vodeći uzrok smrtnosti u svijetu, a prema dobi standardizirana prevalencija moždanog udara u ljudi od 65 godina starosti naviše iznosi 46-72 na 1000 te populacije[3]. Prema rezultatima više studija, ishemijski moždani udar prevladava kao podtip i odgovoran je za 67%-81% svih moždanih udara, a njegova jednomjesečna smrtnost je oko 16%[3]. Godine 1990. moždani je udar bio šesti vodeći uzrok invalidnosti i onesposobljenosti, a predviđa se da će 2020. godine biti na četvrtom mjestu[4]. Cijena koštanja liječenja po bolesniku nakon ishemijskog udara za vrijeme trajanja života iznosi 60.000-230.000 USD[5].

U Hrvatskoj 2000. godine među deset vodećih uzroka smrti moždani udar (nespecificiran kao krvarenje ili ishemijski infarkt) nalazi se na prvom mjestu sa 6.614 umrlih (13.2%) i sa stopom smrtnosti od 151/100.000 stanovnika[6]. Probir na tri izravna uzroka moždanog udara, tj. na hipertenziju, srčane aritmije i COD, uz primarnu prevenciju najvažniji je dio strategije za smanjenje tereta moždanog udara[7].

Karotidna endarterektomija (KEA) i nove endovaskularne karotidne intervencije (karotidna balonska angioplastika */carotid balloon angioplasty*, CBA/ sa stentingom ili bez njega */carotid artery stenting*, CAS/) imaju prvenstveno preventivan koncept u sveukupnom pristupu liječenja moždanog udara, te nalaze svoje mjesto u sekundarnoj prevenciji. Njihov je cilj sprječavanje akutnog i težeg recidivnog ishemijskog moždanog udara, s njim povezanog teškog invaliditeta i smrti, ali i sprječavanje prolaznih disfunkcija

superior to the natural course of the disease as well as to best possible medicamentous therapy with modification of risk factors for atherosclerosis, and that longterm outcome results in improved quality of life and prolonged life expectancy.

Over the 50 years of its use in practice[8,9], CEA has proved its efficiency and durability in the prevention of stroke in symptomatic as well as asymptomatic stenoses. Numerous international prospective randomized studies supported by multidisciplinary consensus reports and *ad hoc* professional association reports[10-17] have emphasized and elaborated its value. Today, CEA is the best scientifically validated method of treatment in vascular surgery.

Yet, over the last few years, the trend in indications for CEA has been observed to change. The effect of general and local anesthesia on CEA outcome has been investigated. The dispute about justifiability of indications for CEA and CAS in asymptomatic carotid disease has heated up. The Asymptomatic Carotid Atherosclerosis Study (ACAS)[11] has been strongly criticized. Urgent CEA is becoming an ever greater challenge for vascular surgeons and neurologists.

In 25 years of its presence, CBA has been technically improved by stenting (at first for recurrent stenoses, then recommended as a routine procedure for all carotid stenoses, and enthusiastically as an alternative to conventional CEA), and later by a number of devices for cerebral protection[18,19]. All these have increased the complexity of the procedure and cost of intervention. In the lack of scientific clinical validation, longterm results, and with fast technological development and competition of numerous products, this endovascular approach has posed many questions about the future trends in the management of carotid stenoses. To date, results of five randomized studies have been published, two of them prematurely discontinued for poor results and complications, allegedly because of inadequate training of the participants, whereas one small study lacked due credibility. The only large study, CAVATAS[20], found no difference in excessive combined rates of stroke and mortality between CEA and CAS, whereas local complications were more frequent in CEA. The SAPPHIRE trial included high risk patients. Concerning complications, only a significantly higher rate of cardiac infarctions was recorded in CEA in comparison with CAS. This study also had to be prematurely discontinued for inadequate patient recruiting, and the results have not yet been published[21]. New studies have been launched, however, their results can only be expected in a few years.

The aim of this presentation is to illustrate our experience and results obtained with CEA, to discuss the

mozga. Racionalan je zahtjev da rezultati liječenja moraju biti bolji od prirodnog tijeka bolesti i najboljeg mogućeg medikamentnog liječenja s modifikacijom rizičnih čimbenika za aterosklerozu, te da dugoročni ishod rezultira poboljšanjem kvalitete života i produženjem životnog vijeka.

Karotidna endarterektomija je kroz 50 godina postojanja[8,9] dokazala svoju učinkovitost i trajnost u prevenciji moždanog udara kod simptomatskih, ali i asimptomatskih stenoza. Mnoge su međunarodne, prospektivne, randomizirane studije poduprte izvještajima multidisciplinskih konsenzusa i *ad hoc* odbora strukovnih udruženja[10-17] istaknule i razjasnile njenu vrijednost. KEA je danas najbolje znanstveno valorizirana metoda liječenja u vaskularnoj kirurgiji.

Ipak, posljednjih se godina zapaža promjena trenda u indikacijama za KEA. Ispituje se utjecaj opće i lokalne anestezije na ishod KEA. Zaoštrila se je rasprava o opravdanosti indikacije za KEA i CAS u asimptomatskoj karotidnoj bolesti. Teške kritike doživljava ACAS (Asymptomatic Carotid Atherosclerosis Study)[11]. Urgentna KEA postaje sve veći izazov za vaskularne kirurge i neurologe.

Kroz 25 godina postojanja karotidna balonska angioplastika (CBA) je tehnički unaprijeđena stentingom (prvo za opetovane stenoze, zatim je preporučena kao rutina za sve karotidne stenoze i entuzijastički kao alternativa za konvencionalnu KEA), a nakon toga i s brojnim napravama za cerebralnu zaštitu[18,19]. To je sve povećalo složenost zahvata i cijenu koštanja intervencije. U nedostatku znanstvene kliničke valorizacije, dugoročnih rezultata, brzog tehnološkog razvoja i kompeticije mnogobrojnih proizvoda ovaj je endovaskularni pristup nametnuo mnoga otvorena pitanja o budućnosti liječenja karotidnih stenoza. Do danas su objavljeni rezultati ukupno pet randomiziranih studija od kojih su dvije prerano prekinute zbog loših rezultata i kom-plikacija, navodno zbog neprimjerene uvježbanosti sudio-nika, a treća je mala studija neuvjerljiva. CAVATAS, jedina veća studija[20], nije našla razlike u previsokim kombiniranim stopama moždanog udara i smrtnosti između KEA i CAS, dok su lokalne komplikacije bile češće kod KEA. Studija SAPPHIRE je uključila visoko rizične bolesnike. Od kom-plikacija jedino je zabilježeno značajno više srčanih infarkta kod KEA (u usporedbi s CAS). I ova je studija prerano prekinuta zbog premalog broja prikladnih bolesnika, a rezultati još nisu objavljeni[21]. Pokrenute su i nove studije, ali na njihove rezultate treba pričekati nekoliko godina.

Cilj ovoga rada je prikazati naša dosadašnja iskustva i rezultate s KEA, raspraviti sadašnje stanje u tom području

present state in this field of vascular surgery with special reference to indications for CEA, and to outline some guidelines for further work.

Material and Methods

At the Department of Vascular Surgery, Sestre milosrdnice University Hospital, Zagreb, Croatia, 2342 CEA procedures were performed in 2223 patients (119 or 5.4% of bilateral operations) from January 1970 till August 31, 2004. There were 692 (31.1%) women and 1531 (68.9%) men, mean age 65.8±9.3 (range 38-98) years. The results recorded so far have been successively reported[22]. Over the last 5 years, the number of operations has been on a steady increase, with a mean of 160 procedures *per* year.

During the last 7 years, preoperative patient preparation included arteriography (DSA) in only 24% of cases. Using appropriate ultrasonographic studies (CDFI, Power Doppler, qualitative plaque analysis, TCD, vasoreactivity testing and HITS recordings), arteriography is only indicated in multiple localization of the disease, proximal disease of the aortic arch, and in symptomatic patients with borderline or poorly assessable degree of stenosis on duplex. Brain computed tomography (CT) is included in routine examination, especially in patients with fixed neurologic deficit and confounded clinical picture.

At our Department, CEA has always been restrictively and selectively indicated in asymptomatic stenoses as well as in symptomatic stenoses after a completed stroke[22,23]. During the last two years, the number of CEA indicated in asymptomatic patients has considerably decreased, while the number of these procedures after transient ischemic attacks (TIA) has increased; in this indication, we tend to perform it within an interval not exceeding 6-8 weeks. Our experience with ischemic stroke in evolution, regressive and minor stroke, and acute major stroke is rather limited. The procedure was indicated in hospitalized patients with a known potential cause (ICA thrombosis following arteriography or CEA), and not later than 6 hours of the symptom onset. Unstable ischemic neurologic syndromes such as crescendo TIA and fluctuating ischemic neurologic deficit have are not present in our casuistics. Indications for CEA according to symptoms are presented in Table 1.

Until October 14, 2002, all procedures were carried out in general anesthesia with selective to routine use of temporary intraluminal shunting (USCI shunt of an adequate diameter). Since October 14, 2002, the majority of operations (about 90%) have been performed in locoregional

vaskularne kirurgije, osobito s obzirom na indiciranje KEA, te naznačiti smjernice za daljnji rad.

Materijal i metode

U razdoblju od siječnja 1970. do 31. kolovoza 2004. godine na Odjelu za vaskularnu kirurgiju KB «Sestre milosrdnice» ukupno je učinjeno 2342 KEA na 2223 bolesnika (119, odnosno 5,4% obostranih operacija). Operirane su 692 (31,1%) žene i 1531 (68,9%) muškarac. Srednja dob operiranih bila je 65,8±9,3 raspon od 38-98 godina. O dosadašnjim rezultatima redovito smo izvještavali[22]. U posljednjih 5 godina broj operacija je u stalnom porastu, s prosjekom od oko 160 operacija na godinu.

U posljednjih sedam godina u prijeoperacijskoj obradi bolesnika arteriografija (DSA) je rabljena u samo 24% slučajeva. Uz odgovarajuću ultrasonografsku obradu (CDFI, Power Doppler, analizom kvalitete plakova, TCD, testiranjem vazoreaktivnosti i registracijom HITS), arteriografiju indiciramo samo kod višestruke lokalizacije bolesti, proksimalne bolesti grana luka aorte, te kod simptomatskih bolesnika s graničnim ili teško procjenjivim stupnjem stenoza na dupleksu. Kompjutorizirana tomografija (CT) mozga spada u rutinsku obradu, osobito kod bolesnika s fiksiranim neurološkim deficitom i zbunjujućom kliničkom slikom.

Mi smo uvijek restriktivno i selektivno indicirali KEA kod asimptomatskih stenoza, ali i onih simptomatskih nakon završenog moždanog udara[22,23]. U posljednje dvije godine znatno opada broj KEA indiciranih u asimptomatskih bolesnika, a povećan je broj operacija nakon prolaznih ishemijskih napadaja (*transient ischemic attack*, TIA) koje nastojimo operirati u razmaku ne dužem od 6-8 tjedana. S ishemijskim moždanim udarom u evoluciji, regresivnim i manjim moždanim udarom te s akutnim velikim moždanim udarom imamo vrlo ograničena iskustva. Operacije smo indicirali samo kod već hospitaliziranih bolesnika s poznatim mogućim uzrokom (tromboza ICA nakon arteriografije ili KEA) i najkasnije do 6 sati od nastupa simptoma. Nestabilni ishemijski neurološki sindromi, kao crescendo TIA i fluktuirajući ishemijski neurološki deficit nisu zastupljeni u našoj kazuistici. Indikacije za KEA prema simptomima prikazane su na tablici 1.

Sve su operacije do 14. listopada 2002. godine izvedene u općoj anesteziji uz selektivnu do rutinsku upotrebu privremenog intraluminalnog premoštenja (USCI shunt primjerenog promjera). Od 14. listopada 2002. godine najveći broj operacija (oko 90%) izveden je u lokoregionalnoj anesteziji, a naš je Odjel uključen u multicentrično ran-

Table 1. Indications for CEA: 1970 – August 31, 2004 (N=2342)

Indication	n	%
Asymptomatic stenosis	341	14.5
Symptomatic stenosis (total)	2001	85.44
Amaurosis fugax/retinal artery occlusion	154	7.70
Contralateral symptoms	603	30.13
Ipsilateral symptoms	186	9.29
Vertebrobasilar symptoms	155	7.75
Stroke in evolution	9	0.45
Completed stroke	894	44.68

anesthesia, and our Department has been included in the multicenter, randomized study of the effect of general *versus* local anesthesia on CEA results (the GALA Trial: a randomized trial of General *versus* Local Anesthesia for carotid endarterectomy)[24]. During the past period presented here, various surgical techniques of CEA have been employed (see Table 2).

On open, conventional CEA, a tacking, direct suture was initially most frequently used for arteriotomy closure, whereas since the 1980s, angioplasty with various patch types has been most commonly employed[22]. Eversion CEA has been introduced since 1985[22], and is ever more frequently used now (reduced duration of the procedure, saving accessories using no alloplastic patch, reduced possibility of infection) for all types of carotid bifurcations. Open CEA with patch angioplasty is preferred in women with asymptomatic advanced stenoses with echolucent plaques, and in those with such symptomatic stenoses when the carotid artery lumen is extremely narrow.

Results

Perioperative complications to up to day 30 of CEA are presented according to the incidence of TIA, and of permanent neurologic deficit (stroke) and death. In patients with progressive and acute stroke (only nine patients oper-

Table 2. CEA operative details 1970-2004 (N=2342)

Operative detail	n	%
Conventional CEA	6	76.7
Eversion CEA	46	23.3
Tacking (direct) sutures	522	22.3
Patches	1274	54.3
Shunt	1526	65.2
Drain	2342	100

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domizirano ispitivanje utjecaja opće prema lokalnoj anesteziji na rezultate KEA (The GALA Trial: a randomised trial of General versus Local Anaesthesia for carotid endarterectomy)[24]. U proteklom vremenu rabili smo različite kirurške tehnike KEA (vidi tablicu 2.).

Kod otvorene, konvencionalne KEA u početku smo najčešće za zatvaranje arteriotomije rabili izravan šav (*tacking, direct suture*), a od osamdesetih godina najčešće angioplastiku različitim vrstama zakrpa (*patch*)[22]. Od 1985. godine uvedena je everzijska KEA[22] koju sada sve češće rabimo (skraćeno trajanje operacije, ušteda potrošnog materijala neuporabom aloplastične zakrpe, manja mogućnost infekcije) kod svih oblika karotidne bifurkacije. Otvorenoj KEA s *patch* angioplastikom prednost dajemo kod žena s asimptomatskim uznapredovalim stenozama s eholucentnim plakovima, kao i s istovrsnim simptomatskim stenozama kada je lumen karotidnih arterija izrazito uzak.

Rezultati

Perioperacijske komplikacije do 30 dana nakon KEA iskazane su prema incidenciji prolaznog (TIA) i trajnog neurološkog deficita (moždani udar), te smrti operiranih.

U bolesnika s progresivnim i akutnim moždanim udarom (samo 9 operiranih) zabilježili smo katastrofalne rezultate sa smrtnošću od 22,2% (dva umrla od 9 operi-

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Drain	2342	100

ated on) disastrous results with a 22.2% mortality rate (two deaths of nine patients operated on) and 55.5% stroke-death rate were recorded. Based on such poor results, we believe that in our circumstances indicating CEA for acute stroke is quite injudicious. Better results can be achieved by treatment at neurologic intensive care units. At our Department, best results were achieved when operating on asymptomatic stenoses. There were no lethal outcomes, whereas 30-day postoperative stroke rate was 0.3% (1/341), and of TIA 0.9% (3/341).

We operated on 1098 (46.9% of total) patients with symptomatic stenoses following TIA. In these patients, the cumulative rate of stroke and death during the perioperative period of observation was 1% (0.5% each or 5/1098), and of TIA 0.7% (8/1098).

CEA upon stroke completion was performed in 894 (38.4% of total) patients. The cumulative rate of stroke (1.8%, 16/894) and death (1.3%, 12/894) was 3.1%, and of TIA 1.1% (10/894).

The cumulative stroke and death rate for all patients operated on was 1.9% (44/2342).

The cumulative rate of associated neurologic (transient and permanent) deficit and mortality for all patients operated on was 2.9% (67/2342), and for those with symptomatic stenoses (clinical stage II, III and IV cerebrovascular disease) 3.1% (63/2001).

Discussion

Discussing the results of CEA achieved in particular cohorts by vascular surgery teams from an institution may appear trivial, however, our results definitely keep abreast of the best ones. We believe that this is so because of proper preoperative preparation, proper candidate selection for CEA, meticulous surgical technique, and appropriate work of the anesthesiologists.

Discussion about the indications for CEA deserves due attention, especially in asymptomatic carotid stenoses, as there is still much controversy on the issue.

The Veterans Affairs Cooperative Study Group (VA)[10] and Asymptomatic Carotid Atherosclerosis Study (ACAS)[11] confirmed the benefit of CEA in preventing the risk of neurologic deficit in asymptomatic carotid stenoses >60% according to NASCET criterion[12] (corresponding to >77% stenoses according to ESCT criterion). ACAS failed to achieve a statistically significant difference in the prevention of stroke in women or of severe, debilitating stroke between medicamentously treated patients and those treated by CEA. The absolute 5-year reduction in

ranih) i stopom smrti od moždanog udara od 55,5%. Zbog takvih rezultata, u našim okolnostima smatramo da indikacija za KEA u akutnom moždanom udaru nije razumna. Bolji se rezultati mogu postići liječenjem u jedinicama intenzivne neurološke skrbi.

Najbolje smo rezultate postigli operirajući asimptomatske stenoze. Nismo imali smrtnih ishoda, a stopa moždanog udara do 30 dana nakon operacije iznosila je 0,3% (1/341) te prolaznog neurološkog deficita (TIA) 0,9% (3/341).

Operirali smo 1098 (46,9% svih operiranih) bolesnika sa simptomatskim stenozama nakon TIA. U tih je bolesnika stopa moždanog udara i smrti u opserviranom perioperacijskom razdoblju iznosila 1% (po 0,5% svakoga, odnosno 5/1098), a prolaznog neurološkog deficita 0,7% (8/1098).

Nakon završenog moždanog udara operirali smo ukupno 894 (38,4% svih operiranih) bolesnika, a stopa moždanog udara (1,8%, 16/894) i smrti (1,3%, 12/894) iznosila je 3,1%, dok je prolazni neurološki deficit zabilježen u 10 (1,1%) bolesnika.

Ukupna stopa moždanog udara i smrti za sve operirane iznosila je 1,9% (44/2342).

Kombinirana stopa udruženog neurološkog (prolaznog i trajnog) deficita i smrtnosti za sve operirane iznosila je 2,9% (67/2342), a za sve operirane sa simptomatskim stenozama (II., III. i IV. klinički stadij cerebrovaskularne bolesti) 3,1% (63/2001).

Rasprava

Već je trivijalna rasprava o rezultatima KEA u pojedinim serijama koje su postigli timovi vaskularnih kirurga neke ustanove, ali svakako naši rezultati spadaju među najbolje. Smatramo da je za to zaslužna dobra prijeoperacijska obrada, dobar odabir kandidata za KEA, minuciozna kirurška tehnika, te dobar rad anesteziologa.

Pozornost zaslužuje rasprava o indikacijama za KEA, osobito kod asimptomatskih karotidnih stenoza koje su i dalje kontroverzne.

Izvješće Veterans Affairs Cooperative Study Group (VA)[10] i studija pod naslovom The Asymptomatic Carotid Atherosclerosis Study (ACAS)[11] potvrđuju dobrobit KEA u prevenciji rizika neurološkog deficita kod asimptomatskih karotidnih stenoza većih od 60% prema kriteriju NASCET[12] (odgovara stenozama >77% prema kriteriju ECST). U studiji ACAS nije zabilježena statistički značajna razlika za prevenciju moždanog udara u žena, kao ni za prevenciju teškog onesposobljavajućeg moždanog udara u usporedbi medikamentno liječenih bolesnika i onih

the risk of ipsilateral stroke and death by 5.9% implies that about 17 patients should be operated on to prevent a single ipsilateral stroke and death over 5 years. One-year reduction of stroke alone by 2% to 1% *per* year[11] means that approximately 20 procedures should be done in asymptomatic patients to prevent a single stroke over a 5-year period. The American Heart Association (AHA) issued recommendations (A degree) in 1995, 1998 and 2001[16,17,25], stating that the only demonstrated indication for CEA in asymptomatic stenoses >60% (according to NASCET criterion) is if the perioperative risk of stroke and death is less than 3%, this in patients life expectancy of at least 5 years. It is suggested that CEA in asymptomatic advanced stenoses be exclusively performed by experienced and recognized teams, and that those patients be identified and operated on in whom the one-year stroke risk is estimated to >4%. Obviously, the criterion risk assessment only the basis of stenosis percent, and possibly on the presence of massive plaque ulceration, or on the existence of contralateral stenosis/obliteration does not appear to be adequate. Not even in 2003 was the beneficial effect of CEA in the management of advanced asymptomatic carotid stenoses properly scientifically verified or demonstrated, but numerous operations have been carried out all over the world and with very satisfactory results. On the one hand, it has been concluded that operative intervention and angioplasty on asymptomatic carotid arteries do not prevent debilitating stroke, on the contrary, that in some well designed studies the operation caused more strokes than it prevented, and that antilipid therapy (pravastatin) efficaciously prevents at least 50% of strokes due to asymptomatic carotid stenoses, is well tolerated and safe[26]. On the other hand, it has been concluded that the intervention is mandatory in patients with asymptomatic stenoses provided a favorable life expectancy, with selection of candidates at a high risk of stroke based primarily on duplex sonography plaque features[27], which is more important than the estimated degree of stenosis. Finally, the results of two studies we have long been waiting for have been published. The aim of the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study was to upgrade risk stratification by use of clinical and ultrasonography factors which, along with the degree of stenosis, have a considerable impact on this risk[28]. The study included 1058 patients with asymptomatic stenoses (ECST 50%-99%) and follow-up of 0.5-5 years. The type of plaque (Geroulakos' classification[29]) was found to be a more significant predictor of the risk of ipsilateral stroke than stenosis degree. Duplex ultrasonography study of plaque density in com-

nakon KEA. Apsolutno smanjenje rizika od istostranog moždanog udara i smrti od 5,9% za petogodišnje razdoblje znači da bi trebalo operirati oko 17 bolesnika kako bi se spriječio jedan istostrani moždani udar i smrt kroz pet godina. Jednogodišnje smanjenje samo moždanog udara od 2% do 1% na godinu[11] zapravo znači da bi trebalo izvesti približno 20 operacija kod asimptomatskih bolesnika kako bi se spriječio jedan moždani udar kroz razdoblje od pet godina. AHA (American Heart Association) je 1995., 1998. i 2001. godine[16,17,25] donijela preporuku (stupnja A) o tome da je jedina dokazana indikacija za KEA kod asimptomatskih stenoza >60% (prema kriteriju NASCET), ako je perioperacijski rizik moždanog udara i smrti manji od 3%, i to kod bolesnika s očekivanim životnim vijekom od najmanje pet godina. Pledira se da kod asimptomatskih uznapredovalih stenoza zahvat KEA izvode samo timovi dokazane uspješnosti te da se operiraju i identificiraju oni bolesnici kod kojih se jednogodišnji rizik moždanog udara procijeni većim od 4%. Očito je nedostatan kriterij procjene rizika koji se uglavnom osniva na postotku stenoze, eventualno na prisutnosti velike ulceracije plaka ili postojanju i kontralateralne stenoze/obliteracije. Niti do 2003. godine[26,27] nije bilo dovoljno znanstveno potvrđeno ni evidentirano da je profilaktična KEA blagotvorna u liječenju uznapredovalih asimptomatskih karotidnih stenoza, ali je učinjeno puno operacija svuda po svijetu s vrlo zadovoljavajućim rezultatima. S jedne je strane zaključeno da kirurška intervencija i angioplastika na asimptomatskim karotidnim stenozama ne sprječavaju onesposobljavajući moždani udar, nego da je, naprotiv, u nekim dobro provedenim studijama kirurgija uzrokovala više moždanih udara nego što ih je spriječila, te da antilipidna terapija (pravastatin) učinkovito sprječava najmanje 50% moždanih udara zbog asimptomatskih karotidnih stenoza, da se takva terapija dobro podnosi i da je sigurna[26]. S druge pak strane, zaključeno je kako postoji mandat za intervenciju kod bolesnika s asimptomatskim stenozama, ako je njihov očekivani životni vijek dobar, uz odabir kandidata s visokim rizikom moždanog udara temeljen prvenstveno na dupleks sonografskim značajkama plakova[27], koja je važnija od procijenjenog stupnja stenoze. Konačno su objavljeni dosadašnji rezultati dviju dugo čekanih studija. Studija ACSRS (Asymptomatic Carotid Stenosis and Risk of Stroke) imala je za cilj poboljšati dosadašnju stratifikaciju rizika upotrebom kliničkih i ultrazvučnih činitelja koji, uza stupanj stenoze, znatno utiču na rizik[28]. Studija je uključila 1058 bolesnika s asimptomatskim stenozama (50%-99%, ECST) s razdobljem praćenja od 0,5 do 5 godina. Ustanovljeno je da je vrst plaka (Geroulakosova klasifikacija[29]) značajniji predskazatelj

bination with computer assisted image analysis and gray scale median (GSM) calculation revealed the hypoechogenic, soft plaques with low GSM (10-25) to correlate well with the incidence of cerebral events. Using the ACSRS model of risk stratification, in >60% stenoses only 20% of patients with a 5-year cumulative risk of stroke could be identified from 21% (4.2% risk *per* year) of those who could be recommended CEA. Using the ACSRS criteria, two-thirds of low risk patients could be saved unnecessary operation, while only 6 operations are needed to prevent a single stroke over 5 years.

Another study, the Asymptomatic Carotid Surgery Trial (ACST), has recently been published in The Lancet[30]. In asymptomatic patients below age 75, with ³70% stenoses assessed by ultrasonography (many of them were on aspirin, antihypertensive and statin therapy), immediate CEA halved the 5-year risk of stroke (in comparison with those allocated to medicamentous, delayed treatment) from 12% to 6% (including the 3% perioperative hazard). A half of this 5-year benefit included severe or fatal stroke. The benefit did not refer to those older than 75, of whom a half died during the 5-year period from unrelated causes. The authors note that inappropriate patient selection and less sophisticated operative technique may preclude such a beneficial impact of CEA when performed elsewhere, i.e. not at the institutions included in the study.

Comparing the results of ACAS and ACST trials it appears that there is no substantial difference between the ultimate benefit from surgical treatment of asymptomatic stenoses and that from most appropriate medicamentous therapy, and that we are still quite far from the scientifically based and generally accepted criteria for patient selection for CEA.

There is no need to discuss about indicating CEA for symptomatic stenoses, as these indications have been widely adopted upon completion of some large studies[12-17], especially NASCET and ECST.

Patients with major, debilitating stroke should be advised conservative treatment at neurologic intensive care units, and indications for CEA should be considered after 4-6 weeks.

Our early results and observations about the effect of locoregional anesthesia on CEA outcome will be reported in separate.

rizika istostranog moždanog udara od stupnja stenoze. Dupleks ultrasonografsko ispitivanje gustoće plaka u kombinaciji s računalnom analizom slike i računanjem medijana sive skale (GSM) pokazalo je kako hipoehogeni, meki plakovi s niskim vrijednostima GSM (10-25) dobro koreliraju s incidencijom moždanih događaja. Primjenom modela ACSRS za stratifikaciju rizika kod stenoza >60% može se identificirati samo 20% bolesnika s petogodišnjim kumulativnim rizikom moždanog udara od 21% (godišnji rizik 4,2%), kojima se može preporučiti KEA. Uz primjenu kriterija ACSRS dvije trećine bolesnika s malim rizikom mogu biti pošteđeni nepotrebne operacije, a potrebno je samo 6 operacija da se spriječi jedan moždani udar kroz pet godina.

Druga je studija, ACST (Asymptomatic Carotid Surgery Trial), nedavno objavljena u Lancetu[30]. Kod asimptomatskih bolesnika mlađih od 75 godina, sa stenozama od 70% i više procijenjenih pomoću UZV (mnogi od njih bili su i na aspirinu, antihipertenzivnoj i statinskoj terapiji) neposredna KEA je prepolovila petogodišnji rizik moždanog udara (u usporedbi s onima koji su bili na medikamentnoj, odgođenoj terapiji) s 12% na 6% (uključen perioperacijski rizik od 3%). Polovica od ove petogodišnje koristi odnosila se je na teški ili smrtonosni moždani udar. Korist se ne odnosi na osobe starije od 75 godina od kojih u petogodišnjem razdoblju umre polovica zbog nevezanih uzroka. Napominje se kako izvan ustanova uključenih u studiju neodgovarajući odabir bolesnika i loša kirurška tehnika mogu osujetiti takovu dobrobit KEA.

Uspoređujući rezultate studija ACAS i ACST čini se da nema bitne razlike u konačnoj dobrobiti kirurškog liječenja asimptomatskih stenoza prema dobrobiti najbolje medikamentne terapije, te da smo još uvijek daleko od znanstveno dokazanih i općeprihvaćenih kriterija za odabir bolesnika za KEA.

O indikacijama za KEA kod simptomatskih stenoza ne treba raspravljati, jer su one opće prihvaćene nakon provedenih multicentričnih studija[12-17], poglavito studija NASCET i ECST.

Bolesnicima s velikim, onesposobljavajućim moždanim udarom treba preporučiti konzervativno liječenje u jedinicama intenzivne neurološke skrbi, a nakon 4-6 tjedana razmotriti indikaciju za KEA.

O ranim rezultatima i našim zapažanjima o utjecaju lokoregionalne anestezije na ishod KEA posebno ćemo izvijestiti.

Conclusion

Carotid endarterectomy is the most commonly performed vascular operation worldwide. According to epidemiologic data, it is estimated that there are 3,800 symptomatic and 30,000 asymptomatic patients in Croatia, whereas the annual CEA/CAS requirements amount to 3,200 procedures. Vascular surgeons in Croatia perform only 15% of these requirements[31].

Upon publication of the results of multicenter, prospective, randomized studies CEA seemed to be confirmed as a gold standard in the prevention of stroke, especially in symptomatic patients with hemodynamically significant stenoses, and also in symptomatic patients, which was supported by consensus[16,17,25]. In contrast to practice with a great number of operations performed in asymptomatic patients with favorable results, studies have shown the evidence for CEA benefit in these patients to be questionable or minimal. The arguments for preventive CEA in asymptomatic patients are that 5%-12% of so-called 'silent strokes' could be verified by CT in these patients, that not many strokes are predicted by TIA, and that not all "asymptomatic" patients, likewise the "symptomatic" ones, are identical. For example, ocular TIA carries a lower risk of hemispheric symptoms and stroke, whereas some "symptomatic" patients present with vertebrobasilar symptoms although otherwise free from evident stenoses of the respective basin. This discussion generally points to a conclusion that categorization of patients candidates for CEA, which is based solely on the degree of stenosis and presence or absence of neurologic symptoms is not precise enough to reliably assess the real risk in each individual patient. Recent studies (ACST and ACSRS)[28,30] have shed additional light upon the issue of indicating CEA in asymptomatic patients, however, they have also opened some new questions.

The future of the management of carotid stenoses is difficult to predict. In the present phase of development, an efficacious method of surgical therapy for COD and stroke prevention is available and its possibilities should certainly be properly utilized. The future of endovascular approach (CBA/CAS) should not be competition to CEA but the methods should be considered complementary, however, they require scientific validation, just like CEA.

Zaključak

Svuda u svijetu KEA je najčešće izvođena vaskularna operacija. Prema epidemiološkim podacima procijenjeno je da u Hrvatskoj ima 3.800 simptomatskih i više od 30.000 asimptomatskih bolesnika, te da prosječna godišnja potreba za KEA/CAS iznosi 3.200 zahvata na godinu. Vaskularni kirurzi u Hrvatskoj obave samo 15% realnih potreba[31].

Nakon objavljivanja rezultata multicentričnih, prospektivnih, randomiziranih studija činilo se je da je KEA potvrđena kao zlatni standard u prevenciji moždanog udara, osobito u simptomatskih bolesnika s hemodinamski značajnim stenozama, ali i kod asimptomatskih, što je potkrijepljeno konsenzusima[16,17,25]. U konfliktu s praksom da se je velik broj operacija s dobrim rezultatima izvodio na asimptomatskim bolesnicima, studije su pokazale kako su upitni ili minimalni dokazi za dobrobit KEA kod ovih bolesnika. Argumenti za preventivnu KEA u asimptomatskih bolesnika bili su da se u njih CT-om mozga može verificirati 5%-12% tzv. "tihih moždanih udara" i da ima malo moždanih udara nagoviještenih kroz TIA, te da svi "asimptomatski" bolesnici nisu isti, kao što nisu isti niti svi oni "simptomatski". Na primjer, očni TIA nosi manji rizik od hemisfernih simptoma i moždanog udara, a neki se "simptomatski" očituju vertebrobazilarnim simptomima, iako su bez očitih stenoza tog sliva. Iz cijele rasprave nameće se zaključak da je kategorizacija bolesnika kandidata za KEA koja se temelji samo na stupnju stenoze i prisutnosti ili odsutnosti neuroloških simptoma nedovoljno precizna za procjenu stvarnog rizika u svakog bolesnika. Više svjetla u problem indikacija za KEA kod asimptomatskih bolesnika donijele su novije studije (ACST i ACSRS)[28,30], ali su otvorena i nova pitanja.

Budućnost liječenja karotidnih stenoza teško je predvidjeti. U sadašnjoj fazi razvoja raspoloženo učinkovitom metodom kirurškog liječenja karotidne okluzivne bolesti i prevencije moždanog udara, te svakako treba iskoristiti sve njene mogućnosti. Budućnost endovaskularnog pristupa (CBA/CAS) ne bi trebala biti kompeticija zahvatu KEA, nego komplementarnost, ali i te metode treba znanstveno valorizirati kao i KEA.

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CAROTID SURGERY IN 2004: STATE-OF-THE ART, PROGNOSES AND PROSPECTS
KAROTIDNA KIRURGIJA 2004: STANJE, PROGNOZE I PERSPEKTIVA

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Carotid surgery is not a simple organ surgery. This is the surgery of soul and personality for its solving complex psychophysical problems in patients with cerebral ischemia. However, it is the most thoroughly investigated area of surgery, subjected to the meticulous criteria of evaluation. Carotid surgery has become a prototype for the EBM. Continuous investigations have been performed for the last 50 years[1-3], with surgeons investigating it together with neurologists; one can find a great number of prospective studies of each particular segment of carotid surgery; strict Quality Control has been established at Centers of Excellence; patients are followed up by use algorithms and multidimensional facilities; stable Cost/Benefit and Cost/Effectiveness relationships are well known for CEA and CAS; and the highest number of consensuses has been published just in carotid surgery[4-6]. If we assume such analysis in some other medical branches, very soon we would come to the open question of their use in the contemporary medical treatment. Carotid surgery has a significant influence upon the most important today's characteristic of Vascular Surgery, the patients' QOL[7,8].

Carotid Epidemiology in Croatia

In Croatia, there are 10,000 strokes/year. In the total number of atherosclerotic deaths, stroke accounts for 33%. Over 8100 strokes are ischemic (44% infarct, 21% TIA, 21% embolization). Atherothrombosis causes 4900 strokes/year. The total costs of stroke in Croatia are 120 million USD/year. In the USA, the costs of CEA are 8500 USD, while the costs of the major stroke are 34,000 USD in the first year, and 18,000 USD every next year. The costs of CEA in Croatia are 700 USD![9-12]

What is the real extent of the problem? Knowing that we have 0,08% TIA/stroke patients and 1500 asymptomatic patients *per* 200,000 population, we can easily calculate that in Croatia there are about 3800 symptomatic and 34,000 asymptomatic patients with carotid occlusive disease (COD). According to the EBM supported calculations of the need of 38-99 CEA/100,000, in Croatia we need

Karotidna kirurgija nije jednostavna kirurgija organa. To je kirurgija osobnosti i duše, jer rješava složene psihofizičke probleme bolesnika s cerebralnom ishemijom. Najistraženije je područje kirurgije, podvrgnuto strogim kriterijima evaluacije. Karotidna kirurgija postala je prototip za medicinu poduprtu dokazima (EBM*). Istražuje se neprekidno 50 godina[1-3]. U suradnji s neurolozima izvedeno je najviše prospektivnih istraživanja na ovom polju, napravljeno je više prospektivnih, randomiziranih studija svakog segmenta karotidne kirurgije, ustanovljena je stroga kontrola kvalitete u Centrima izvrsnosti, bolesnici se algoritamski i višedimenzijski prate doživotno, uspostavljeni su čvrsti odnosi troška i dobitka (*cost/benefit*) i troška i učinka (*cost/effectiveness*) za KEA/KAS, napravljeno je najviše konsenzusa baš u karotidnoj kirurgiji[4-6]. Ako pretpostavimo ovakovu analizu u nekim drugim granama medicine, ostalo bi otvoreno pitanje opsega njihove današnje primjene.

Karotidna kirurgija ima značajan utjecaj na najvažniju značajku današnje vaskularne kirurgije, a to je kvaliteta života operiranih bolesnika[7,8].

Epidemiologija karotidne bolesti u Hrvatskoj

U RH imamo do 10.000 MU na godinu i u ukupnom broju aterosklerotskih smrti udio MU je 33%. Preko 8100 MU su ishemijski (44% infarkt, 21% TIA, 21% embolizacije). Aterotromboza uzrokuje 4900 MU na godinu. Ukupni troškovi MU u RH iznose 120 milijuna USD na godinu. U SAD troškovi KEA iznose 8500 USD, dok troškovi većeg, završenog MU iznose 34000 USD prve godine, a zatim svake slijedeće godine po 18000 USD. Troškovi KEA u RH iznose 4000 kn![9-12].

Koliki je stvarni problem? Na 200.000 stanovnika ima 0,08% bolesnika s TIA/MU i 1500 asimptomatskih bolesnika. U RH, dakle, ima oko 3800 simptomatskih bolesnika s karotidnom bolešću (COD) i oko 10 puta više asimptomatskih bolesnika (oko 34.000). Sukladno izračunima o 38-99 potrebnih KEA/100.000 stanovnika, u RH je potrebno napraviti 1800-4500 KEA svake godine. Prosječna potreba bi bila 3200 operacija (0,07% KEA na broj stanovnika).

1800-4500 CEA/year. Thus, the average need is 3200 operations (0.07 CEA/population). Framed with the acessible possiblities, the Croatian vascular surgeons can meet 15% of the real needs for CEA each year.

Key Points

In the year 2004, carotid surgery has to consider mutual links of the following:

- patient selection
- evaluation and preoperative care
- operative treatment
- postoperative care

All these lead us to lowering of the stroke/death rate, improvement of the patient's QOL, diminishing the percentage of restenosis, prolonged life expectancy, and rise in the cost/effectiveness of carotid surgery. The historical cost/benefit question of how many CEA procedures we need to perform to prevent one death or stroke has now been answered by the lately published studies. In patients with 80%-99% stenosis, we need to perform 5.6 CEAs to prevent one death/stroke. This is, of course, under the condition that CEA is performed by a team who have reported their own stroke/death rate of 1%-2%. So, in comparison with other surgical branches, CEA is a very cost/benefit procedure. Considering lowering of the costs, we should keep in mind that only 1% of lesions are beyond ultrasound analysis, that routine angiography contributes to decision making in less than 2% of patients, that leaning on duplex does not interfere with the operation success, that the widespread use of LRA is common today[13,14], that strictly indicated CAT scan analysis contributes to lowering of the postoperative complications, and that the length of hospital stay is significantly shortened from 8 to 3-5 days. CFD and MIA analyses are efficacious in the CEA quality control and also diminish the risk of preoperative care to the minimum[15]. TCD points out dysfunction of the circle of Willis and circulatory reversion. Brain CT scan should be used when there is suspicion of a tumor or infarct, in the acute stage of stroke, to differentiate scars from hemorrhagic transition, colliquation or leukoariaosis. It is also useful in search for the true asymptomatic patients[15].

Patient selection

Prospective randomized studies 1980-2004 have led us to the need of multidisciplinary, multicenter EBM consensuses regarding surgical therapy of carotid atherosclerosis[16]. So, EBM has been implanted in the carotid field. The data concerning carotid surgery should be interpreted by the

Ograničeni mogućnostima, vaskularni kirurzi u Hrvatskoj mogu podmiriti 15% stvarnih potreba za KEA.

Ključne točke

Karotidna kirurgija 2004. mora uzimati u obzir međusobnu povezanost:

- izbora bolesnika za kirurgiju
- evaluacije i prijeoperacijske pripreme
- liječenja operacijom
- poslijeoperacijskog liječenja

Sve ovo vodi ka smanjenju perioperacijskog udjela MU i smrtnosti (*stroke/death rate*), unaprijeđenju bolesnikove QOL, smanjenju postoka ponovljene stenoze, produljenju očekivane duljine života i povećanju C/E karotidne kirurgije.

Na povijesno C/B pitanje koliko treba napraviti CEA da bi se spriječila jedna smrt ili MU odgovoreno je objavom rezultata ACST. U bolesnika s 80%- do 99%-tnom stenozom UKA, pod uvjetom da operaciju izvodi tim koji ima stopu s/d od 1%-2%, potrebno je napraviti 5,6 CEA da bi se spriječila jedna smrt ili MU. U usporedbi s drugim granama kirurgije CEA je, dakle, vrlo isplativa operacija. U ***smanjenju troškova*** treba misliti na to da samo 1% lezija nadilazi mogućnosti dupleks analize, da rutinska arteriografija doprinosi odluci u manje od 2% bolesnika, da oslanjanje na dupleks ne utječe na uspjeh operacije, da je na potezu široka upotreba LRA[13,14], da indicirana upotreba CT analize doprinosi smanjenju poslijeoperacijskih komplikacija i da je duljina hospitalizacije značajno skraćena s 8 na 3-5 dana. CFD i MRA su učinkovite prilikom ***kontrole kvalitete KEA*** i smanjuju rizik prijeoperacijske obrade na minimum[15]. TCD ukazuje na disfunkciju Willisova kruga i obrat cirkulacije. CT mozga treba rabiti kod sumnje na tumor ili infarkt, u akutnoj fazi MU, da se razluči ožiljke od hemoragijske tranzicije, kolikvacije i leukoariaoze, te da se pronađu stvarno asimptomatski bolesnici[15].

Izbor bolesnika

Prospektivne randomizirane studije (1980.-2004.) dovele su nas do potrebe multidisciplinskih, multicentričnih EBM konsenzusa u odnosu na kiruršku terapiju karotidne ateroskleroze[16]. I tako je EBM ujahala u karotidno polje. Podatke koji se odnose na karotidnu kirurgiju treba tumačiti u granicama kategorije dokaza i razine preporuka (Ellis i sur., BMJ 1998.), ali u nedostatku najjačih dokaza (dokazi prve razine), čestom u kliničkoj medicini, svaki kirurg treba biti oprezan i oslanjati se na vlastite epidemiološke i perioperacijske rezultate[17-19].

Categories of Evidence and Strength of Recommendation (Ellis *et al*., BMJ 1998), however, in the lack of strong evidence (level 1 evidence), which is by no means rare in clinical practice, each surgeon should be cautious and lean on his own epidemiologic and perioperative results[17-19].

We can discriminate several groups of patients as follows:

- symptomatic patients
- asymptomatic patients
- patients in advanced age
- patients suitable for urgent/emergent CEA
- patients suitable for surgical therapy of stroke in evolution
- patients for surgical therapy of a completed stroke
- patients who need surgical therapy for TIA/stroke from external carotid artery (ECA)

Symptomatic patients with the atherosclerotic origin of the disease from carotid artery benefit from CEA according to international agreement. Operative indications in this group are hemispheric TIA, contemporary monocular blindness, and minor stroke with good recovery. CEA in ICA stenosis >70% offers absolute stroke reduction by 17% in 2 years and 40% in 3 years (NASCET/ECST). In centers with perioperative stroke/death rate <5%, all symptomatic patients with 70% stenosis should be operated on.

Asymptomatic patients have come forward when it has recently been found that CEA/CAS are successfully used in *stroke prevention*[4,12,20]. The International Overseas Consensus Statements have made a step forward and introduced *qualitative* besides exclusively quantitative plaque analysis used until that time[21-24]. The selection criteria for asymptomatic patients are: >75% bifurcation stenosis, asymptomatic stenosis progression, GSM 25-31, silent stroke CAT/MRI confirmed, insufficient collateralization, ACA collapse, reversed circulation or PSV lowering on TCD, and patients with carotid occlusive disease and multifactorial risk (smoking, hypertension, cholesterol). The causes that subject a patients to the risk of CEA are refractory, prolonged hypertension, preoperativne neurologic deficit, nephropathy, angina and cardiac arrhythmia. The factors that contribute to the patient selection are: elevated serum VEGF-2R (in asymptomatic patients significantly falls after CEA)[25], elevated TAT, ATIII, t-PA and D-dimer tests, MES on TCD (18% asymptomatic patients are MES positive). Impaired cognitive functions are improved in 28% of asymptomatic patients after CEA.

Elderly patients have less opportunity to benefit from carotid surgery. CEA is cost/effective up to the age of 75.

Bolesnike dijelimo na:

- simptomatske
- asimptomatske
- bolesnike starije dobi
- one za urgentnu/emergentnu CEA
- one pogodne za kiruršku terapiju MU u razvoju
- one za kiruršku terapiju završenog MU
- one kojima treba kirurška terapija TIA/MU iz VKA

Simptomatski bolesnici s aterosklerotskim izvorištem bolesti iz karotidne arterije imaju koristi od KEA prema međunarodnom konsenzusu. Indikacije u ovoj skupini su hemisferni TIA, privremena monokularna sljepoća, manji MU s dobrim oporavkom. CEA u stenozi UKA >70% ima apsolutno smanjenje MU za 17% u 2 godine i 40% u 3 godine (NASCET/ECST), pa u centrima s perioperacijskom stopom s/d <5% treba operirati simptomatske bolesnike sa 70%-tnom stenozom.

Asimptomatski bolesnici izbili su u prvi plan kada je nedavno utvrđeno da se KEA/KAS uspješno upotrebljavaju za sprječavanje MU[4,12,20]. International Overseas Consensus Statements napravili su korak naprijed i uveli kvalitativnu uz dosadašnju isključivo kvantitativnu analizu plaka[21-24]. Kriteriji izbora za operaciju asimptomatskih bolesnika su: stenoza >75% smještena na karotidnoj bifurkaciji s progresijom u UKA, progresija asimptomatske stenoze, GSM 25-31, "tihi MU" potvrđen CT/MRI analizom, nedovoljna kolateralizacija moždane cirkulacije, kolaps SMA, reverzni protok ili usporenje protoka na TCD i bolesnik s KOB i kombinacijom činitelja rizika (pušenje, hipertenzija, povišen kolesterol). Uzroci povećanja rizika od KEA su refraktorna, višegodišnja hipertenzija, prijeoperacijski neurološki deficit, nefropatija, pektoralna angina i značajna srčana aritmija. Činitelji koji doprinose izboru asimptomatskih bolesnika za operaciju su: povišeni serumski VEGF-2R u asimptomatskih bolesnika značajno pada nakon KEA[25], zatim povišenje TAT, ATIII, t-PA i D-dimera, MES otkrivene pomoću TCD (18% asimptomatskih bolesnika su pozitivni za višestruke znakove embolije (*multiple embolic signs*, MES). Oštećenje kognitivnih funkcija se poboljšava u 28% asimptomatskih bolesnika nakon KEA.

Stariji bolesnici imaju manje prilike uživati u dobrobiti karotidne kirurgije. CEA je C/E do 75 godina života. Simptomatski bolesnici od 75-80 godina selektivno se odabiru za zahvat ako imaju očekivanu duljinu života do 5 godina. U ovoj i starijoj skupini CEA se radi u asimptomatskoj fazi ako je dokazana progresija bolesti u stenozi od <80% do >80% ili ako je dokazana za život opasna komplikacija plaka[26,27].

Symptomatic patients aged 75-80 are selected if their life expectancy is 5 years. In this and older age groups, CEA should be preformed in the asymptomatic stage if the disease progression is documented in <80% to >80% stenosis, or if the patient has a life-threatening plaque complication[26,27].

Urgent/emergent CEA is still controversial and a subject of discussion. There are neither EBM supported facts to support it nor prospective, randomized trials from this area. However, numerous multicenter reports lead us to the following recommendations: *emergent CEA* should be performed in patients with perioperative thrombosis or stroke, in thrombosis/stroke after angiography/CAS, if the patient has severe stenosis and stroke in evolution or crescendo TIAs. *Urgent CEA (within 48 hours)* should be performed in patients with flotating thrombus, frayed plaque, or plaque fracture. There is no indication for emergent/urgent CEA in patients with good and fast recovery of the neurologic deficit originating from carotid thrombosis[28] (Table 1).

In patients with completed stroke CEA can be performed if minor, fixed neurologic deficit is caused by a high-grade stenosis (the risk of recurrence or infarct progression is 20% within 6 weeks). If there is no hemorrhagic transition, CEA is recommended to be done 11-15 days after stroke[7].

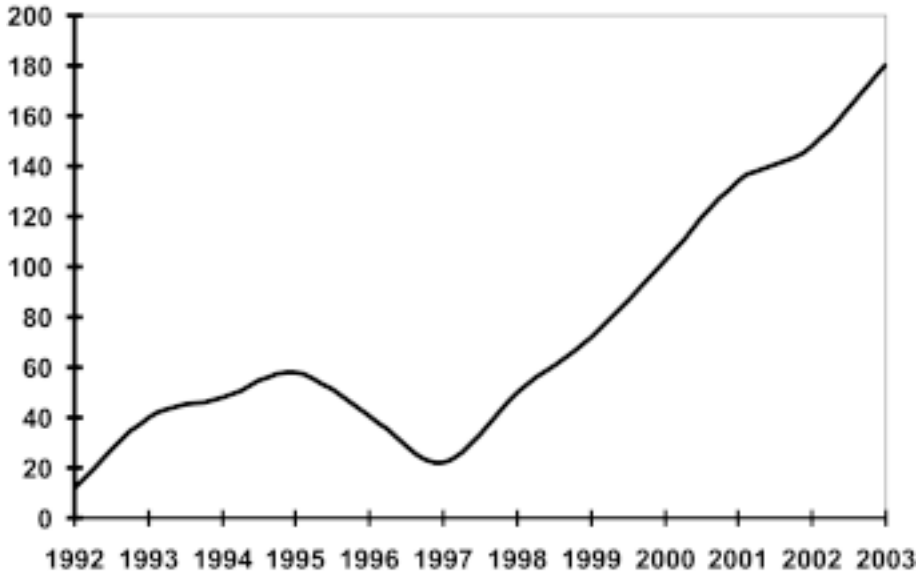
In TIA or stroke from the ECA, which gives 3% of the cerebral flow, neurologic deficit is caused by embolization, and not by hypoperfusion. Amaurosis fugax and nonspecific ipsilateral symptoms are frequent. Emboli enter through periorbital, leptomeningeal, occipital, dural and

Urgentna/emergentna KEA još je uvijek proturječno područje za raspravu. Nema jasnih EBM činjenica koje bi ju podupirale, kao ni prospektivnih, randomiziranih studija iz ovog područja. Ipak, brojni multicentrični izvještaji vode nas do slijedećih preporuka: emergentnu (neposrednu) KEA treba izvesti u bolesnika s perioperacijskom trombozom/MU, u trombozi/MU nakon arteriografije/CAS, ako bolesnik ima jaku stenozu i MU u razvoju/krešendo TIA. Urgentnu KEA (unutar 48 sati) treba izvesti u bolesnika s flotirajućim trombom, s razlistanim plakom i u bolesnika s frakturom plaka. Nema indikacije za emergentnu/urgentnu KEA u bolesnika s brzim oporavkom neurološkog deficita nastalog zbog karotidne tromboze[28] (tablica 1.).

U bolesnika sa završenim MU KEA se izvodi ako je manji, fiksni neurološki deficit uzrokovan visokim stupnjem stenoze ili predokluzivnom stenozom (rizik od recidiva ili proširenja infarkta je 20% unutar 6 tjedana). Ako nema hemoragijske tranzicije infarkta, KEA je preporučljiva 11-15 dana nakon MU[7].

Kod TIA/MU iz VKA koja nosi 3% moždanog protoka neurološki ispadi nastaju zbog embolizacije, a ne hipoperfuzije. Česti su *amaurosis fugax* i nespecifični ipsilateralni simptomi. Embolusi ulaze kroz periorbitalne, lemptomeningealne, okcipitalne, duralne i hipoglosalne kolaterale u bazen UKA. Endarterektomija UKA i VKA je metoda izbora. Ako je UKA okludirana, isključuje se, a VKA se nakon endarterektomije pokriva zakrpom[7].

Fig. 1. Number of CEA at Merkur University Hospital 1992-2003
Slika 1. Broj KEA u Kliničkoj bolnici Merkur 1992.-2003.



Tablica 1. Rezultati na Ljestvici težine neuroloških ispada (NESS) nakon urgentne/emergentne KEA u Kliničkoj bolnici Merkur

	Zadovoljavajuće	Nezadovoljavajuće	Smrt
SIE (10)	8	2	0
NDAO (20)			
KEA <3 h (18)	15	2	1
CEA >3 h (2)	1	1	0
CTIA (6)	5	1	0
AC (16)	14	2	0

SIE=moždani udar u evoluciji, NDAO=neurološki deficit uzrokovan arterijskom okluzijom, CTIA=*crescendo* prolazni ishemijski napadaji (TIA), AC=anatomska pitanja, KEA=karotidna endarterektomija

Table 1. Neurologic Events Severity Score (NESS) after urgent/ emergent CEA at Merkur University Hospital

Result	Satisfactory	Unsatisfactory	Death
SIE (10)	8	2	0
NDAO (20)			
CEA <3 h (18)	15	2	1
CEA >3 h (2)	1	1	0
CTIA (6)	5	1	0
AC (16)	14	2	0

SIE=stroke in evolution, NDAO=neurologic deficit caused by artery occlusion, CTIA=crescendo TIA, AC=anatomical considerations, CEA=carotid endarterectomy

hypoglossal collaterals in the ICA pool. Endarterectomy of the ICA and ECA is the method of choice. If the ICA is occluded, the best method is its exclusion, while ECA is endarterectomized and patched[7].

Patient evaluation and preoperative care

After the first CEAs based on ultrasound (US) in 1979, in the last 15 years the rapid development of noninvasive diagnostics has contributed to the establishment of the new "gold standard". Since 1995, the non-operator dependent criteria for US and computed tomography (CT) diagnosis have been set up[15]. Health Care Commissions started approving US Centers of Excellence. CFD, Power Doppler, GSM and TCD offer us qualitative analysis of the COD including determination of the degree of stenosis. SonoCT, carotid CAT scan and XRES-CFD technology depict the future of the preoperative carotid diagnosis[29-31]. CFD charactheristics that indicate CEA irrespective of symptoms are:

- stenosis >70%
- ulceration or ulcer thrombosis
- thrombosis of the stenotic site
- echolucency (GSM 25-32)
- soft-core or lypoid plaque
- plaque hemorrhage
- frayed plaque

Parameters that enable non-operator dependent criteria on CFD devices are: PSV, measurement of the degree of stenosis and GSM. We could propose the following formula for the *non-operator dependent criteria score (NODCSc)* as an indicator for CEA:

$$\text{NODCSc} = \frac{\text{degree of stenosis}}{\text{GSM}}$$

Evaluacija i prijeoperacijska priprema

Nakon prvih KEA na temelju UZV dijagnostike 1979. godine, posljednjih 15 godina brzi razvoj neinvazivne dijagnostike doprinosi ustanovljenju novog "zlatnog standarda". Od 1995. postavljeni su subjektivno neovisni kriteriji UZV i CT dijagnostike (*non-operator dependent criteria*)[15]. Health Care Commissions su započele odobravanje ultrazvučnih Centara izvrsnosti. CFD, Power Doppler, GSM i TCD daju kvalitativnu analizu karotidne bolesti uz određivanje stupnja stenoze. SonoCT, CT karotidnih arterija i tehnologija XRES-CFD zacrtavaju budućnost prijeoperacijske karotidne dijagnostike[29-31].

Značajke CFD koje indiciraju KEA bez obzira na simptome su:

- stupanj stenoze >70%
- ulceracija plaka
- tromboza u ulkusu ili mjestu stenoze
- eholucentnost (GSM 25-32)
- mekan (*soft-core*) ili lipemični plak
- krvarenje u plak
- razlistanost plaka

Parametri koji omogućuju uspostavu subjektivno neovisnih kriterija na CFD uređajima su: mjerenje brzine protoka, mjerenje stupnja stenoze i određivanje GSM. Prijedlog *non-operator dependent criteria score(NODCSc)* kao indikacije za KEA mogao bi biti:

$$\text{NODCSc} = \frac{\text{stupanj stenoze}}{\text{Grey Scale Median}}$$

NODCSc >2,4 = apsolutna indikacija za KEA (70/25)
NODCSc >2,0 = indikacija za KEA 60/30)
NODCSc < 20 = mogućnost BMT (60/40)

NODCSc >2.4 = absolute indication for CEA (70/25)
NODCSc >2.0 = CEA could be indicated (60/30)
NODCSc <2.0 = BMT is the favorite option (60/40)

Angiography should be used when CCA stenosis is present, in smooth stenosis, in unequivocal CFD findings and when CFD laboratory is not reliable, in patients who cannot stand MRA, and when there is a clear indication for CAS[15].

There is no trustworthy method for predicting the perioperative mortality and stroke. *Ischemic tolerance of the brain parenchyma* could be assumed but not predicted. Xenon CAT scanning with the acetazolamide tolerance test seems to be a useful method for determining the group at risk of stroke during CABG. LRA is becoming the "gold standard" in the treatment of patients with uncertain ischemic tolerance during CEA[32-34].

Operative treatment

CEA should be performed in:

- asymptomatic patient if the operator's stroke/death rate is <2%
- symptomatic patient if the operator's stroke/death rate is <5%
- using a gentle, detailed technique
- using intraoperative US quality control
- using the most realiable neurologic monitoring

LRA during CEA is the best neurologic monitoring. During the procedure, the cerebrovascular reflexes are spared, the need of shunting is reduced 5 times, the incidence of hematoma is 10 times lower, the rate of nerve injury is 11 times lower, perioperative mortality fell from 1.3% to 0%, the incidence of stroke is by 0.3% lower, hospital stay is reduced 2 times, the CEA costs are by 35% lower and brain perfusion is improved (reports 2002/2003)[13,14].

Eversion CEA (ECEA) is an acceptable alternative in the hands of a surgeon who have learned the method under a mentor supervision, at institutions that follow the CEA results with CFD and at hospitals that have published results harmonized with the existing ECEA studies. ECEA is indicated in patients prone to restenosis (CEA 5.2%, ECEA 2.5% EVEREST 1996/2000), in patients with distal stenosis but not at the skull base, if contralateral flow is not impaired, and if there are no radiologic signs of cerebral infarction[35,36].

An important alternative to CEA is percutaneous transluminal carotid angioplasty (PTCA). In the years 1995/1997, PTCA carried an 8%-10% stroke/death rate, 10%-

Arteriografiju treba upotrebljavati kod stenoze CCA, pri glatkoj restenozi, kod kontroverznih CFD nalaza i nepouzdanog CFD laboratorija, u bolesnika koji ne podnose MRA i ako postoji indikacija za CAS[15].

Ne postoji sigurna metoda za predviđanje perioperacijske smrtnosti i MU. *Ishemijska tolerancija moždanog parenhima* može se pretpostaviti, ali ne i sigurno predvidjeti. Skeniranje pomoću Xenon CT s testom tolerancije na acetazolamid korisna je metoda za određivanje rizične skupine za razvoj MU u tijeku CABG. LRA postaje zlatni standard za liječenje bolesnika s nesigurnom tolerancijom ishemije u tijeku KEA[32,33,34].

Liječenje operacijom

KEA treba napraviti:

- u asimptomatskog bolesnika ako je stopa s/d operatera<2%
- u simptomatskog bolesnika ako je stopa s/d operatera <5%
- preciznom, detaljističkom i nježnom tehnikom
- upotrebom intraoperacijske UZV kontrole
- upotrebom najpouzdanijeg neurološkog monitoringa

LRA prilikom KEA jest najbolji neurološki monitoring. Za vrijeme operacije očuvani su cerebrovaskularni refleksi, smanjuje potrebu za *shuntom* 5 puta, incidencija hematoma manja je 10 puta, ozljeda kranijskih živaca 11 puta, peripoperacijska smrtnost je smanjena s 1,3% na 0%, za 0,3% je manja incidencija MU, skraćuje boravak u bolnici 2 puta, pojeftinjuje cijenu operacije do 35% i povećava perfuziju mozga (izvještaji 2002./2003.)[13,14].

Everzijska KEA prihvatljiva je inačica liječenja u rukama kirurga koji je izučio metodu pod nadzorom mentora u ustanovama koje prate rezultate KEA CFD analizom i u bolnici koja objavljuje rezultate u skladu s rezultatima postojećih studija EKEA. EKEA je indicirana u bolesnika sklonih stvaranju restenoze (KEA 5,2%, EKEA 2,5% EVEREST 1996./2000.), u bolesnika s distalnom stenozom ali ne do baze lubanje, ako je očuvan kontralateralni karotidni protok i ako nema CT/MRI znakova za moždani infarkt[35,36].

Važna inačica operacijske tehnike je i perkutana transluminalna karotidna angioplastika (PTKA). U godinama 1995./1997. PTKA je nosila 8%-10% stope s/d, 10%-15,7% neuroloških komplikacija i 16% rane restenoze u 6 mjeseci[37]. Zbog toga je uveden karotidni stenting (KAS) i 1998. je stopa s/d iznosila 3%-4,7%, a druge neurološke komplikacije 4,6%-6,3% nakon primarnog stentinga. Krajem 1990-ih, razvile su se metode cerebralne zaštite (CPD) i

15.7% rate of neurologic complications and 16% rate of restenosis in 6 months[37]. Therefore, carotid stenting (CAS) took place and in 1998 the stroke/death rate was 3%-4.7%, and the rate of other neurologic complications 4.6%-6.3% after primary stenting. By the end of the 1990s, the cerebral protection devices (CPD) were developed and the dilemma between CAS and PTCA was solved. CAS lowered the rate of neurologic complications down to 0.5%[38,39]. However, CAS is always perforemd in a *selected group of patients* and is far from suitable for all CEA candidates. According to the 1999-2003 consensuses, CAS is not suitable for patients with a low risk of CEA, when there is a long petrified carotid lesion, if intraluminal thrombus exists, in patients with recent stroke or crescendo TIAs, in tortuous arteries, if there is no access for CAS, if stent or CPD cannot be applied, or if there is combined CCA and ICA stenosis[40,41]. The n*umber of embolic particles* freed during CAS is directly related to the plaque GSM value and is significantly higher in patients with GSM <25. Such patients have a 71.4% rate of periprocedural complications, whereas in patients with GSM >50 the complication rate is 7.2%. Yet, it should be noted that embolic events in the GSM >50 group, when present, are more disastrous due to the bigger embolic particles. When we bear in mind that the GSM in the interobserver analysis is complementary in more than 89% of patients, and that GSM findings are completely complementary to histology in 46% of patients, we must admit that *plaque morphology significantly influences the patient prognosis as well as the CEA/CAS indications*[22]. CEA *vs* CAS studies in small groups of patients showed better results in CEA groups if the patients were not selected. But, when the patients were selected for CAS, the results were equal[21,41]. According to the current criteria, *not every carotid disease should be subjected to angioplasty, and the selection criteria for CAS should not be identical with those for CEA.* Indications for CAS are:

- stenoses of the supraaortic branches
- patients at high risk
- high ICA stenosis
- hostile neck
- smooth stenosis
- patients with short life expectancy[42]

Within 5 years, stent fractures as well as in-stent stenoses and occlusions are noticed. Comparative studies of CEA and CAS after carotid restenosis showed the mortality in both groups was 0%. However, the CAS group had 16% of TIAs (CEA 0%), 18% of in-stent restenoses in 3 years, and in 7.5% of patients the stent had to be surgically removed within 3 years[43,44].

više nije bilo dvojbe oko izbora KAS/PTKA, jer je KAS sa CPD smanjio neurološke komplikacije do 0,5%[38,39]. Ipak, KAS se primjenjuje *u izabranoj skupini bolesnika* i daleko je od pogodnosti za sve kandidate za KEA. Prema konsenzusima 1999.-2003. KAS nije prikladan: ako imamo bolesnika niskog rizika za KEA, za dugu kalcificiranu leziju karotide, ako postoji intraluminalni tromb, u bolesnika sa svježim CVI ili *crescendo* TIA, ako postoje tortuozne arterije, ako je otežan pristup za KAS ili ako se ne može postaviti stent ili CPD te ako postoji udružena stenoza ZKA i UKA[40,41]. *Broj embolijskih čestica* oslobođenih za vrijeme KAS izravno je povezan s GSM pripadnog plaka i značajno je veći za bolesnika s GSM <25. U takovih bolesnika razvija se 71,4% periproceduralnih komplikacija, za razliku od 7,2% komplikacija u bolesnika s GSM >50. Ipak, treba reći da su, kada nastupe, embolijski događaji teži u skupini s GSM >50%, jer se u ovoj skupini oslobađaju veće embolijske čestice. Kada uzmemo u obzir da je podudarnost GSM analize u analizi među promatračima veća od 89% i da je GSM analiza potpuno sukladna patološko-anatomskoj analizi u 46% bolesnika, treba reći da *morfologija plaka značajno utječe na prognozu bolesnika i na postavljanje indikacije za KEA ili KAS*[22]. U usporedbi KEA i KAS metode rezultati na manjim skupinama bolji su u skupini KEA ako bolesnici nisu selekcionirani. Ako su strogo izabrani za KAS, rezultati usporedbe KEA i KAS se podudaraju[21,41].

Prema današnjim kriterijima, *ne treba svaku karotidnu bolest liječiti angioplastikom, a izbor bolesnika za KAS ne bi trebao biti isti kao izbor bolesnika za KEA.* Indikacije za KAS su:

- stenoze supraaortnih grana
- bolesnik visokog rizika
- vrlo visoka stenoza UKA
- vrat nepristupačan za KEA
- glatka homogena stenoza
- bolesnik s kraćom očekivanom duljinom života[42].

Primijećene su frakture stentova unutar 5 godina, kao i *in-stent* stenoze i okluzije stenta. Usporedne studije KEA i KAS nakon restenoze karotidne arterije pokazuju da je smrtnost u objema skupinama 0%. Međutim, skupina KAS ima 16% TIA (KEA 0%), 18% *in-stent* restenoza u 3 godine, a u 7,5% bolesnika trebalo je kirurški ukloniti stent unutar 3 godine od zahvata[43,44].

Kirurgija ima lošije rezultate ako postoji tandemska stenoza, disfunkcija Willisova kruga, udružena koronarna bolest, srčana grješka ili aritmija i trajni neurološki deficit. Serije iz 2003. godine pokazuju da je tromboza UKA rijetko uzrokovana tehničkom grješkom. Uzrok su multisegmentna KOB, duge, kritične stenoze, tandemske lezije i "*string*

Surgery has worse results if there is a tandem stenosis, circle of Willis dysfunction, concomitant coronary disease, heart failure or arrhythmia, and if a permanent neurologic deficit exists. Series from 2003 show that ICA thrombosis is rarely caused by technical failure. The causes of thrombosis appear to be multisegmental COD, longterm critical stenosis, tandem lesions, and the "string sign". In such cases, peri/intraoperative ICA occlusion occurs in 0.8% of patients[45]. It is time for careful revision of the so-called *high-risk patients*. Multicenter analysis of 1906 "high-risk" patients showed a cumulative stroke/death rate of 1.3%, and the results of CEA in high-risk patients were comparable with the low-risk group, especially after LRA reappeared on the scene. At the end, the CEA cost/effectiveness is by far more favorable than that of the routine use of CAS[44,45].

In patients with concomitant coronary and carotid disease (in Croatia there are 8%-10% of such coronary patients), CEA/CAS should be performed under the following criteria[46,47]:

- stable angina in high-risk patient = CAS
  in low-risk patient = CEA
- in candidate for PTCoA with COD
  with low cardiac risk = PTCoA, then CEA
  with high cardiac risk = PTCoA and CAS
- in CABG candidate with COD
  if urgent with symptomatic COD = one act pro cedure
  if urgent with asymptomatic COD = one act pro cedure only if COD is bilateral not urgent with symptomatic COD = CAS first, then CABG
  not urgent with asymptomatic COD = CABG first, then CAS or CEA

Conclusion

The number of patients operated on is rising. The number of CEAs perfomed at Merkur University Hospital between 1992 and 2003 is shown in Table 2. The number of CEAs at European and USA centers tells us the state-of-the-art of CEA as a routine and cost/effective procedure, which offers acceptable results and treatment to the nonselected group of patients with COD (Table 3). The percentage of asymptomatic patients in various centers shows us that the real rate of asymptomatic patients that need CEA could be around 30%-40% (Table 4). Perioperative CEA results of the author during the past 3 decades show a continuous decrease in the stroke/death rate in spite of broadening the indication spectrum for CEA from 1976 to 2003 (Table 5).

sign". U ovakovim slučajevima peri/intraoperacijska okluzija UKA događa se u 0,8% bolesnika[45].

Vrijeme je i za pozornu reviziju tzv. *bolesnika visokog rizika*. Multicentrična analiza 1906 bolesnika s "visokim rizikom" pokazala je da je kumulativni sd/r u ovoj skupini 1,3% i da su rezultati KEA u visoko rizičnih usporedni s rezultatima u bolesnika niskog rizika, osobito nakon uvođenja LRA. Na kraju, C/E za KEA kao sigurnog zahvata povoljniji je od rutinske primjene KAS[44,45].

U bolesnika s *udruženom koronarnom i karotidnom bolešću* (u RH ima 8%-10% takovih koronarnih bolesnika) KEA/KAS treba izvoditi prema slijedećim kriterijima[46,47]:

- stabilna angina u bolesnika visokog rizika = KAS
  u bolesnika niskog rizika = KEA
- u kandidata za PTCoA s KOB
  s niskim srčanim rizikom = PTCoA pa KEA
  s visokim srčanim rizikom = PTCoA i KAS
- u kandidata za CABG s KOB
  u hitnoći sa simptomatskom KOB = operacija u jednom aktu
  u hitnoći s asimptomatskom KOB = jedan akt samo ako je KOB bilateralna
  bez hitnoće sa simptomatskom KOB = prvo KAS, potom CABG
  bez hitnoće s asimptomatskom KOB = CABG pa KAS ili KEA.

Zaključak

Na kraju možemo zaključiti da broj operiranih bolesnika sigurno raste. Broj KEA u Kliničkoj bolnici Merkur od 1992. do 2003. prikazan je na slici 1. Broj KEA prema centrima u Europi i SAD pokazuje nam današnje stanje KEA kao rutinske i isplative operacije koja nudi mogućnost izlječenja neselekcioniranoj skupini bolesnika s KOB (slika 2.). Udio asimptomatskih kandidata prema centrima pokazuje kako se stvarni postotak asimptomatskih bolesnika koji trebaju KEA kreće oko 30%-40% (slika 3.). Perioperacijski rezultati KEA prema autorima u tijeku 3 desetljeća pokazuju stalan pad udjela MU i smrtnosti unatoč znatnom proširenju indikacija za KEA od 1976. do 2003. godine (slika 4.).

Otvorena pitanja 2004. su:

- Što učiniti s karotidnom stenozom <50% udruženom s neurološkim deficitom?
- Koje osobine plaka povezati sa stupnjevima neurološkog deficita[24]?
- Kada će poslijeoperacijska CFD kontrola postati standardom[15,33]?

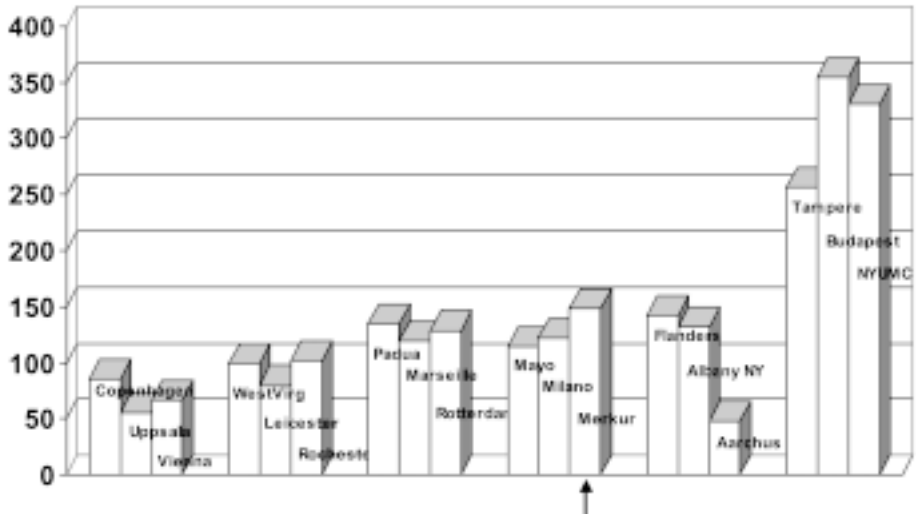


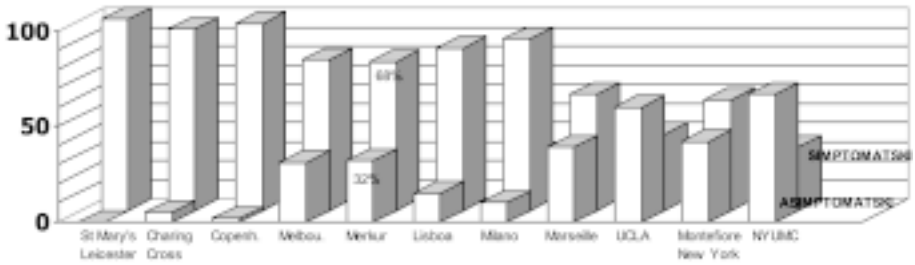
Fig. 2. Number of CEA at institutions in Europe and USA in 2003
Slika 2. Broj KEA u centrima Europe i SAD tijekom 2003. godine

Open questions in 2004 are:

- What to do with carotid stenosis <50% combined with neurologic deficit?
- Which plaque characteristics can be connected with various grades of neurologic deficit[24]?
- When the postoperative CFD control will become a standard[15,33]?
- How can we improve ischemic cerebral protection[13,14,31,33,36,38]?
- How can we predict ischemic tolerance of the brain parenchyma[49]?
- What is the optimal CEA/CAS rate[40]?
- What is the best medical treatment for COD?
- Gene therapy and carotid occlusive disease[48]?
- Clear up the role of the VEGF165 and VEGF121 in preventing the carotid plaque development[25]?
- How to measure the importance of secondary prevention of carotid occlusive disease?
- Kako se može unaprijediti zaštita mozga od ishemije[13,14,31,33,36,38]?
- Kako predvidjeti ishemijsku toleranciju moždanog parenhima[49]?
- Koji je optimalni omjer KEA/KAS[40]?
- Što je *Best Medical Treatment* KOB?
- Genska terapija i KOB[48]?
- Razmotriti razvoj VEGF165 i VEGF121 u sprječavanju razvoja ateromatoznog plaka[25]?
- Odmjeriti važnost sekundarne prevencije KOB?

Tumač kratica: EBM=Evidence Based Medicine, KEA=karotidna endarterektomija, MU=moždani udar, KAS=karotidni stenting, UKA=unutarnja karotidna arterija, VKA=vanjska karotidna arterija, s/d r=stroke/death rate, QOL=Quality of Life, GSM=grey scale median, C/E=cost/effectiveness, C/B=cost/benefit, SMA=srednja moždana arterija, LRA=loko-regionalna anestezija, KOB=karotidna okluzivna bolest, CABG=coronary artery

Fig. 3. Proportion of asymptomatic patients for CEA in international vascular surgery centers in 2003
Slika 3. Udio asimptomatskih bolesnika za KEA prema svjetskim centrima vaskularne kirurgije u 2003.godini



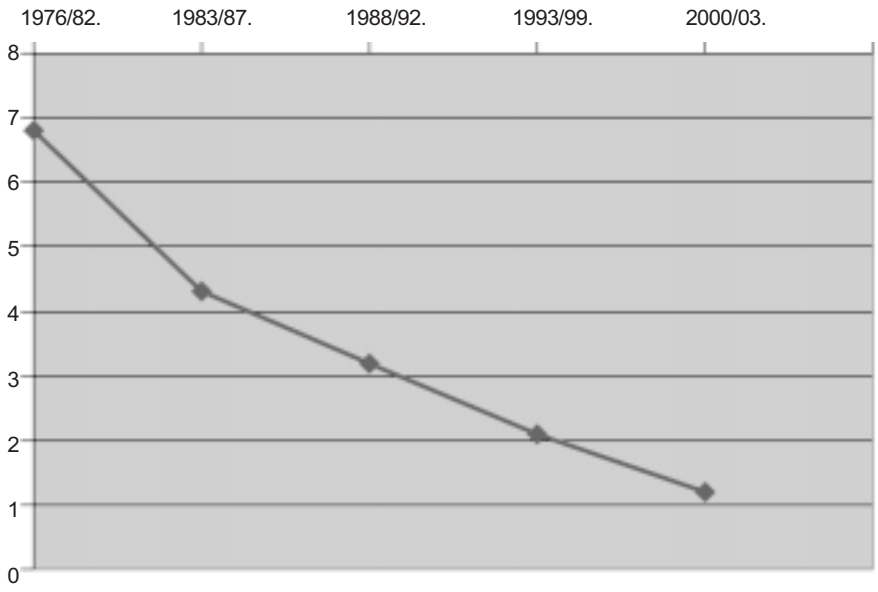


Fig. 4. Perioperative stroke/death rate according to literature reports 1976-2003
Slika 4. Udio perioperacijske smrtnosti i moždanog udara prema literaturnim izvješćima od 1976. do 2003. godine

Abbreviations: EBM=Evidence Based Medicine, CEA=carotid endarterectomy, CAS=carotid stenting, ICA=internal carotid artery, ECA=external carotid artery, s/d r=stroke/death rate, QOL=Quality of Life, GSM=grey scale median, C/E=cost/effectiveness, C/B=cost/benefit, MCA=middle cerebral artery, LRA=locoregional anesthesia, COB=carotid occlusive disease, CABG=coronary artery bypass graft, US=ultrasound, ECEA=eversion carotid endarterectomy, CPD=cerebral protection device, CCA=common carotid artery, PTCoA=percutaneous transluminal angioplasty of coronary arteries, MES=multiple embolic signs, VEGF =vascular endothelial growth factor, CFD=color flow duplex

bypass graft, UZV=ultrazvuk, EKEA=everzijska karotidna endarterektomija, CPD=cerebral protection device, ZKA=zajednička karotidna arterija, PTCoA=perkutana transluminalna angioplastika koronarnih arterija, MES=multiple embolic signs, VEGF=vascular endothelial growth factor, CFD=color flow duplex

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MIGRAINE AND STROKE – IS THERE AN ASSOCIATION?
MIGRENA I MOŽDANI UDAR – POSTOJI LI POVEZANOST?

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Migraine and stroke are neurovascular disorders encountered in practice on a daily basis. The association of migraine and stroke has been postulated since the 19th century, and has been confirmed by recent studies. Individual cases of hemorrhagic stroke in migraineurs have been described, however, their interrelatedness remains questionable and as yet inadequately explored.

The International Headache Society classification of headaches from 1988 was revised in 2004, now including the entity of migrainous infarction (MI) as a subheading (1.5.4) of the heading 1.5 Migraine Complications. This diagnosis refers to the onset of brain infarction during migrainous headache with aura, which has been verified by brain CT or MR[1].

A number of epidemiologic studies of the association between migraine and MI have been conducted worldwide, including clinical, case-control and cohort studies. Based on the results obtained, the authors generally agree that MI occurs very rarely, mostly in young women aged below 45. In one of the latest studies, Abroix *et al.* found only nine cases of MI to be dignosed in a cohort of 2000 patients treated for stroke over a 10-year period, all nine in young women[2,3].

It has not yet been explained why migraine increases the risk of ischemic stroke in young women. Donaghy *et al.* report on a considerably higher risk of MI in individuals suffering from migraine for more than 12 years, provided the headaches have increased in frequency over the past few months. Besides longterm presence and high frequency of migrainous headaches, migraine with aura also increases the risk of MI[4].

Migrena i moždani udar predstavljaju neurovaskularne poremećaje s kojima se svakodnevno susrećemo. Povezanost migrene s moždanim udarom naslućuje se već od 19. stoljeća, a suvremena istraživanja to i potvrđuju. Opisani su i pojedinačni slučajevi hemoragijskog moždanog udara u migreničara, ali njihova međusobna povezanost još uvijek je ostala upitna i nedovoljno istražena.

Klasifikacija glavobolja prema Međunarodnom društvu za glavobolje iz 1988. godine doživjela je reviziju 2004. godine, u kojoj pod točkom 1.5 Komplikacije migrene stoji podtočka 1.5.4. Migrenski infarkt (MI). Ova dijagnoza podrazumijeva nastanak infarkta mozga tijekom migrenske glavobolje s aurom, koji je ujedno potvrđen na CT ili MR mozga[1].

U različitim dijelovima svijeta učinjeno je više epidemioloških ispitivanja koja se odnose na povezanost migrene i MI: kliničke studije, kontrolirane studije i kohortne studije. Autori se na osnovi dobivenih rezultata uglavnom slažu da se MI javlja vrlo rijetko i to uglavnom u mladih žena do 45. godine života. Tako su u jednom od posljednjih epidemioloških ispitivanja Abroix i sur. našli da je u skupini od 2000 bolesnika liječenih zbog moždanog udara tijekom desetgodišnjeg razdoblja dijagnosticirano samo 9 slučajeva MI i to isključivo u mladih žena[2,3].

Zbog čega migrena povećava rizik nastanka ishemijskog moždanog udara u mladih žena još uvijek nije u potpunosti razjašnjeno. Donaghy i sur. navode da su znatno većem riziku za nastanak MI izloženi migreničari koji pate od migrene duže od 12 godina, te ako su glavobolje posljednjih mjeseci postale znatno učestalije. Uz dugotrajnost i učestalost migrenskih glavobolja povećan rizik naročito

Migraine as well as mitral valve prolapse, patent foramen ovale (PFO) and atrial septum aneurysm (ASA) have recently been ever more frequently implicated as the risk factors for stroke. PFO has been found to be the source of embolism leading to MI at a young age. It should be noted that PFO and ASA also are potential vascular causes of migraine with aura, which in turn implies the risk of MI[5].

The risk of migrainous stroke is additionally increased by the use of oral contraceptives that contain high estrogen, then with the presence of diabetes mellitus, hypertension and smoking.

The platelet theory explains the onset of migraine by the platelet-leukocyte interaction, suggesting an association of migraine and stroke at the cellular level[6].

Migraine is a multifactorial as well as a genetic disorder, therefore history, i.e. familial migrainous burden, needs to be carefully considered. In familial hemiplegic migraine, mutations on the CACNA1a gene on chromosome 19 or a mutation on chromosome 1 have been demonstrated. Migraine is usually the first symptom of CADASIL, which in addition to migrainous headaches implies lacunar stroke or transient ischemic attacks and progressive dementia. In this entity, mutations on chromosome 19 have been detected. Current genetic studies have pointed to the genetic basis of association between migraine and MI[7,8].

The clinical picture, course and prognosis of MI have been investigated by many authors. Most of them agree that it is a rare entity, usually with a mild clinical picture and complete or satisfactory recovery. As the disorder does show a tendency of recurrence, the prognosis is good. Thus, MI differs from other ischemic strokes by its occurrence at a young age, female predominance, mild clinical picture, and favorable outcome[9].

Migraine and stroke are neurovascular disorders that appear to bear some association, however, a number of open questions yet remain in the field despite considerable advances in neuroscience and genetics.

predstavlja migrena s aurom[4]. Migrena te prolaps mitralne valvule, otvoreni foramen ovale (PFO) i aneurizma septuma atrija (ASA) u novije vrijeme se sve više spominju kao čimbenici rizika za nastanak moždanog udara. Zapaženo je da PFO predstavlja izvor embolija koje uzrokuju MI u mladoj životnoj dobi. Zanimljivo je da PFO i ASA predstavljaju i mogući vaskularni uzrok za migrenu s aurom koja kao takva predstavlja rizik za nastanak MI[5].

Rizik za nastanak migrenskog moždanog udara dodatno povećavaju oralna kontracepcijska sredstva koja sadrže veće količine estrogena, zatim šećerna bolest, hipertenzija i pušenje.

Trombocitna teorija tumači nastanak migrene interakcijom trombocit-leukocit, ukazujući na povezanost migrene i moždanog udara na staničnoj razini[6].

Migrena je višečimbenski, ali i genetički poremećaj, pa je neobično važno obratiti pozornost na anamnezu, tj. obiteljsku opterećenost migrenom. Kod obiteljske hemiplegične migrene dokazane su mutacije na CACNA 1a genu kromosoma 19 ili pak mutacija na kromosomu 1. Migrena je najčešće prvi simptom CADASIL-a koji uz migrenske glavobolje podrazumijeva lakunarne moždane udare ili prolazne ishemijske napadaje i progresivnu demenciju. Kod ovog entiteta su dokazane mutacije na kromosomu 19. Suvremena genetička istraživanja ukazala su na genetsku podlogu povezanosti migrene i MI[7,8].

Klinička slika, tijek i prognoza MI zaokuplja zanimanje niza autora. Većina ih se slaže kako se radi o rijetkom entitetu koji obično ima blagu kliničku sliku s potpunim ili dobrim oporavkom. Kako se uglavnom ne ponavlja, prognoza mu je dobra. Prema tome, MI se razlikuje od ostalih ishemijskih moždanih udara po tome što se javlja u mlađoj životnoj dobi, češće je zastupljen u žena, ima blagu kliničku sliku i povoljan konačni ishod[9].

Migrena i moždani udar su neurovaskularni poremećaji između kojih postoji povezanost, ali usprkos značajnom napretku neuroznanosti i genetike još uvijek ostaje čitav niz otvorenih pitanja na koja treba naći odgovore.

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EPILEPSY AS A CONSEQUENCE OF STROKE
EPILEPSIJA KAO POSLJEDICA MOŽDANOG UDARA

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Not received / Nije primljeno

VASCULAR DEMENTIA
VASKULARNA DEMENCIJA

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Dementia is a generic term used for the syndrome of gradual deterioration of memory capacity and other intellectual functions accompanied by personality and behavior disorders. Vascular dementia (VD) is the second most common cause of dementia, immediately following Alzheimer's disease (AD), and it includes the dementia caused by ischemic or hemorrhagic lesions of the brain as well as the dementia following states of ischemia and hypoxia associated with heart failure. In order to diagnose VD, it is necessary to establish the causal connection between brain lesion and onset of dementia, which is often impossible in clinical practice.

Vascular dementia accounts for 20% of all cases of dementia, while at the same time in 20% of AD patients there are pathologic changes in the brain characteristic of VD[1]. The incidence and prevalence of VD increase with age, so that the VD prevalence in the population older than 70 is about 3%[2]. VD occurs due to a disorder of blood circulation in the brain and, being of the nature of a vascular disease of the brain, it can manifest clinically in several ways. The most common is the multi-infarct dementia (MID), which progresses gradually or rapidly, following numerous mini-ischemic strokes or transitory ischemic attacks (TIA). This type of dementia is sometimes called cortical type and is manifested clinically as amnesia, agnosia, apraxia or aphasia. The subcortical type of VD is known as Binswanger's disease or syndrome of diffuse infarction of the white matter, where there are diffuse or multifocal areas of

Demencija je zajednički pojam za sindrom postupnog propadanja sposobnosti pamćenja i drugih intelektualnih funkcija praćen poremećajem osobnosti i ponašanja. Vaskularna demencija (VD) je nakon Alzheimerove bolesti (AB) drugi najčešći uzrok demencije, a neuropatološki uključuje demenciju uvjetovanu ishemijskim ili hemoragijskim lezijama mozga, kao i demenciju nakon ishemijsko-hipoksičnih stanja povezanih sa srčanim zatajenjem. Za dijagnozu VD potrebna je prije svega vremenska uzročno posljedična povezanost lezije mozga i nastupa demencije, što često puta u kliničkoj praksi nije moguće utvrditi.

Na vaskularnu demenciju otpada oko 20% svih demencija, dok u još oko 20% bolesnika s AB postoje neuropatološke promjene u mozgu znakovite za VD[1]. Incidencija i učestalost VD raste sa životnom dobi, tako da je učestalost VD u populaciji starijoj od 70 godina oko 3%[2].

VD nastaje zbog poremećaja moždanog krvnog optoka, a zbog naravi vaskularne bolesti mozga može se klinički očitovati na nekoliko načina. Najčešća je multi-infarktna demencija (MID) koja se razvija postupno ili naglo prateći brojne mini-ishemijske moždane udare ili prolazne ishemijske napadaje (TIA). Ovaj tip demencije se katkada naziva kortikalnim tipom, a klinički se očituje kao amnezija, agnozija, apraksija ili afazija. Subkortikalni tip VD je poznat kao Binswangerova bolest ili sindrom difuzne infarkcije bijele tvari, gdje se nalaze difuzna ili višežarišna područja periventrikularne demijelinizacije s gubitkom aksona i reaktivna glioza, što je najčešće posljedica aterosk-

periventricular demyelination with the loss of axons and reactive gliosis, which is most frequently the consequence of atherosclerotic changes in penetrating arteries and arterioles in the white matter. These changes occur in 80% of patients with VD regardless of the cause, and are not rare in AD (15%-50)[3]. It is believed that these changes are associated with arterial hypertension and/or diabetes, and that the syndrome of dementia occurs due to disruption of connections between the cortex and subcortex.

The subcortical type of VD can also occur due to ischemic lesions of lacunae, which besides dementia results in psychomotor reduction, mental obtusion, anhedonia, dysphagia, dysarthria, and walking disorder reminding of parkinsonism. It occurs typically in former or current smokers, with arterial hypertension and/or diabetes.

A strategically positioned single ischemic infarct or hemorrhage can result in a sudden onset of dementia, which is frequently the leading symptom of stroke. This type of dementia is characteristic of a stroke in the angular gyrus of the dominant hemisphere, dorsomedial part of the thalamus of the dominant hemisphere, and infarct in the area of hippocampus.

Risk factors for VD are in the first place age and cerebrovascular disease with all its risks, such as arterial hypertension, smoking, diabetes, hyperlipidemia, etc. If VD occurs in younger patients, hereditary types of cerebrovascular disorders like CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy) should be considered[4].

The diagnosis of VD is based on the occurrence of a cerebrovascular disease and dementia with a history of risk factors for cerebrovascular disease, different focal neurologic signs, and a positive neuroimaging report. Unfortunately, the diagnostic criterion established in such a manner is too flexible and thus allows many variations that are not desirable from the aspect of "evidence based medicine". Therefore several different criteria for the diagnosis of VD have been developed, but unfortunately none of them are universal and without objections[5]. The key role in the diagnosis is played by neuroimaging, especially proton and T2 sequence of brain MRI, where in case of subcortical dementias zones of enhanced signal can be seen periventricularly (leucoaraiosis) or multiple small lesions in basal ganglia and pons.

Differential diagnosis includes other causes of dementia (AD, Lewy body dementia, etc.) but also the conditions like Parkinson's disease, progressive supranuclear paralysis, multisystem atrophies, brain tumors, hydrocephalus, etc.

lerotskih promjena u penetrantnim arterijama i arteriolama u bijeloj tvari. Ove promjene se nalaze u oko 80% bolesnika s VD bez obzira na uzrok, ali nisu rijetke niti kod AB (15%-50%)[3]. Vjeruje se da su ove promjene povezane s arterijskom hipertenzijom i/ili dijabetesom, a da sindrom demencije nastupa zbog prekida veza između korteksa i subkorteksa.

Subkortikalni tip VD može nastati i zbog lakunarnih ishemijskih lezija, što uz demenciju rezultira psihomotornom usporenošću, mentalnom tupošću, anhedonijom, disfagijom, disartrijom, poremećajem hoda koji podsjeća na parkinsonizam itd. Tipično se javlja u bivših ili aktulanih pušača, s arterijskom hipertenzijom i/ili dijabetesom.

Strateški pozicioniran jednokratni ishemijski infarkt ili krvarenje može rezultirati naglim nastupom demencije koja je često vodeći simptom moždanog udara. Ovakav tip demencije znakovit je za moždani udar u angularnom girusu dominantne hemisfere, dorzomedijalni dio talamusa dominantne hemisfere, te infarkt u području hipokampusa.

Rizični čimbenici za nastup VD su prije svega životna dob i cerebrovaskularna bolest sa svim svojim rizicima poput arterijske hipertenzije, pušenja, dijabetesa, hiperlipidemije itd. Ako se VD pojavi u mlađoj životnoj dobi treba razmišljati o nasljednim oblicima cerebrovaskularnih poremećaja poput CADASIL (cerebralna autosomna dominantna arteriopatija sa subkortikalnim infarktom i leukoencefalopatijom)[4].

Dijagnoza VD počiva na prisutnosti cerebrovaskularne bolesti i demencije uz anamnezu rizičnih čimbenika za nastup cerebrovaskularne bolesti, različitim žarišnim neurološkim znacima, te pozitivnom nalazu neurološkog slikovnog prikazivanja. Nažalost, ovako postavljen dijagnostički kriterij je isuviše fleksibilan pa dopušta mnoštvo varijacija koje nisu poželjne sa stajališta "medicine zasnovane na dokazima". Stoga je razvijeno nekoliko različitih kriterija za dijagnozu VD, no nažalost niti jedan nije univerzalan i bez zamjerka[5]. Ključnu ulogu u dijagnostici ima neurološko slikovno prikazivanje, poglavito proton i T2 sekvenca MRI mozga, gdje se u slučaju subkortikalnih demencija vide zone pojačanog signala periventrikularno (leukoaraioza) ili višestruke male lezije u bazalnim ganglijima i ponsu.

Diferencijalna dijagnoza uključuje ostale uzroke demencije (AB, demencija Lewyevih čestica itd.), ali i stanja poput Parkinsonove bolesti, progresivne supranuklearne paralize, multisistemskih atrofija, tumora mozga, hidrocefalusa itd.

Liječenje VD se svodi na prevenciju cerebrovaskularne bolesti i njenih rizika, dok u slučaju postojanja neurološ-

The treatment of VD comes down to the prevention of a cerebrovascular disease and its risks. If there is evidence of neurologic signs, one can consider physical therapy of the motor deficit and walking, treatment of aphasia by a speech pathologist, etc. Concerning specific drugs for the improvement of cognitive functions, they have been proven successful in the symptomatic treatment of cognitive disorders of AD, e.g., donepezil and galantamine, thus a similar effect is also expected in VD, and this has partially been confirmed in clinical studies.

kih znakova u obzir dolazi fizikalna terapija motornog deficita i hoda, logopedsko liječenje afazije itd. Od specifičnih lijekova za poboljšanje spoznajnih funkcija, koji su se pokazali donekle uspješnima u simptomatskom liječenju kognitivnog poremećaja u okviru AB, poput donepezila i galantamina, očekuje se sličan učinak i u VD, što su djelomice potvrdila dosdašnja klinička istraživanja.

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DEPRESSION AND STROKE
DEPRESIJA I MOŽDANI UDAR

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Summary

Cerebrovascular diseases are currently the leading public health problem in industrialized countries, and depression is the fourth major health problem. Today the association between depression and stroke is considered definite. Depression is the most common psychiatric disorder associated with cerebrovascular diseases, occurring in 26% to 34% of patients within two years post-stroke. There is a correlation between the severity of post-stroke depression and localization of cerebral lesion, i.e. the closer the lesion to the left frontal lobe region, the higher the incidence and severity of depression. Early detection and treatment have become the basic goals of modern medicine. Attempts at preventing the development of post-stroke depression have been less successful to date. Treatment is quite successfully performed with the use of psychotherapy, psychopharmacotherapy, electroconvulsive therapy and rehabilitation. The biopsychological model provides an insight into the multifactorial etiology of the mental and physical disorders of post-stroke depression, which is a precondition for comprehensive and fully successful treatment.

Key words: *depression, stroke, epidemiology, diagnosis, antidepressants*

Sažetak

Cerebrovaskularne bolesti predstavljaju danas vodeći zdravstveni problem u zemljama zapadnog svijeta, a depresija je četvrti najveći zdravstveni problem. Danas se smatra da je povezanost između depresije i moždanog udara nedvojbena. Depresija je najčešći psihijatrijski poremećaj povezan sa cerebrovaskularnim bolestima, javlja se u 26 do 34 posto bolesnika unutar dvije godine poslije moždanog udara. Postoji povezanost između težine poslijeinzultne depresije i lokacije lezije mozga: što su oštećenja mozga bliže području lijevog frontalnog režnja, učestalost i težina depresije je veća. Rano otkrivanje i liječenje postaje jedan od temeljnih ciljeva suvremene medicine. Pokušaji sprječavanja razvoja poslijeinzultne depresije dosad su bili manje uspješni. Liječenje se uspješno provodi primjenom psihoterapije, psihofarmakoterapije, elektrokonvulzivne terapije i rehabilitacije. Biopsihološki model omogućuje razumijevanje višečimbenske etiologije psihičkih i fizičkih poremećaja poslijeinzultne depresije kao preduvjeta za sveobuhvatno i uspješno liječenje.

Ključne riječi: *depresija, moždani udar, epidemiologija, dijagnostika, antidepresivi*

Introduction

Depression is a disorder as old as the human race, and occurs as a universal human experience present across all cultures. More than a half of humans have experienced mild depression at least once in life, while not being aware of the disorder. In contrast to transient low mood, when we use to say "Today I feel depressed", however, depression can also be a serious disease. It is considered that 50% of depressed patients remain unrecognized, some 70% are not treated, and only 10% are treated according to current therapeutic principles[1].

Post-stroke depression develops in 26% to 34% of stroke patients representing a major challenge to modern medicine because of its high morbidity, absenteeism, disability and mortality[2]. Depression and cerebrovascular disease cause great distress because of reduced daily, recreative and working abilities.

Early detection and treatment have therefore become one of the main goals of modern medicine.

Epidemiology

Depression has been on an increase worldwide, so that it was the fourth major public health problem in world in 1990, and has been estimated to be the second one in 2020. In women the rate of depression is two-to fourfold that in men. Every fifth woman and every tenth man experience at least one serious depressive episode in their lives. The prevalence of depressive disorders in the general population is 3.6-6.8 or greater in some European countries[1,2]. In Croatia, it is estimated that there are about 200,000 individuals with various depressive disorders. Depression predominates in the 35-60 age groups. The rate of suicide ranges from 10% to 15% in individuals with major depression[1]. The number of depressive disorders has been on a continuous increase during the past and present centuries in all industrialized countries, which is not exclusively attributable to better diagnosis.

Types of depressive disorders

According to etiologic factors:

- primary depressive disorders F32-F39
- secondary, organic or symptomatic depressive disorders F06.3
- depressive reaction to stress; short-term F43.20 or prolonged F43.21

According to clinical picture severity:

- mild depression F32.0
- moderate depression F32.1

Uvod

Depresija je stara koliko i čovječanstvo i javlja se kao univerzalno ljudsko iskustvo prisutno u svim kulturama. Blagu je depresiju doživjelo barem jednom u životu više od polovice čovječanstva, a da pritom mnogi nisu ni znali o čemu se radi. Međutim, depresija može biti vrlo ozbiljna bolest za razliku od prolaznog neraspoloženja kada smo skloni reći «Danas sam depresivna/depresivan». Smatra se da 50 posto depresivnih bolesnika ostaje neprepoznato, da ih se oko 70 posto ne liječi, a da se samo 10 posto depresivnih bolesnika liječi sukladno suvremenim terapijskim načelima[1].

Depresija poslije moždanog udara javlja se u 26 do 34 posto bolesnika i predstavlja značajan izazov za suvremenu medicinu zbog visokog pobola, bolovanja, invaliditeta i smrtnosti[2]. Depresija i cerebrovaskularna bolest u bolesnika izazivaju velike duševne boli zbog smanjenja općih životnih, rekreativnih i radnih sposobnosti. Rano otkrivanje i liječenje postaje jedan od temeljnih ciljeva suvremene medicine.

Epidemiologija

Depresija je u cijelom svijetu u porastu i već je 1990. godine bila na četvrtom mjestu javnozdravstvenih problema u svijetu, a procjenjuje se da će 2020. godine biti na drugom mjestu. Depresija je dva do četiri puta češća u žena nego u muškaraca. Svaka peta žena i svaki deseti muškarac tijekom života dožive barem jednu ozbiljnu depresivnu epizodu. Učestalost depresivnih poremećaja u općoj populaciji je 3,6-6,8 posto ili veća u nekim europskim zemljama[1,2]. Vjerojatno u Hrvatskoj ima oko 200.000 osoba s različitim depresivnim poremećajima. Depresija prevladava u dobi od 35 do 60 godina. Stopa samoubojstva se kreće od 10-15 posto u osoba s velikim depresivnim poremećajem[1]. Broj depresivnih poremećaja je u neprestanom porastu tijekom prošlog i ovog stoljeća u svim razvijenim zemljama, a nije isključivo posljedica bolje dijagnostike.

Vrste depresivnih poremećaja

Prema etiološkim čimbenicima:

- primarni depresivni poremećaji F32-F39
- sekundarni, organski i simptomatski depresivni poremećaji F06.3
- depresivna reakcija na stres; kratka F43.20 ili produžena F43.21

Prema težini kliničke slike depresija se dijeli na:

- blagu depresiju F32.0

- moderate depression with somatic symptoms F32.2
- severe depression with psychotic symptoms F32.3

How to recognize depressive disorder

Depressive disorders manifest with the occurrence of depressive episodes characterized by combinations of a variable number of the mentioned 9 (DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4th Revision)[3] or 10 (ICD 10: International Classification of Diseases – 10th Revision)[4] symptoms. At least 4, 5 and 7 symptoms persisting for at least two weeks are needed to make the diagnosis of mild, moderate and severe depression, respectively.

Table 1. Symptoms of depressive episode according to ICD-10 and DSM-IV

ICD-10	DSM-IV
1 Depressive mood	Depressive mood (1)
2 Loss of interest and pleasure	Decreased interest and satisfaction (2)
3 Reduced energy or increased fatigue	Fatigue or lack of energy almost daily (6)
4 Loss of self-confidence and self-esteem	Feeling of worthlessness or guilt (7)
5 Inappropriate feeling of self-reproach or guilt	
6 Recurrent thoughts of death or suicide	Recurrent thoughts of death or suicide (9)
7 Difficult thinking and concentration; uncertainty	Difficult thinking and concentration (8)
8 Agitation or retardation almost daily (5)	Agitation or retardation
9 Sleep disturbances	Insomnia or hypersomnia (4)
10 Loss of appetite and body weight change	Significant weight loss or weight gain by more than 5% (3)

In diagnostic algorithm, mental and somatic diseases should be taken in consideration and ruled out by differential diagnosis, e.g., thyroid diseases, Parkinson's disease, dementia, and exhaustion of coping abilities. It is estimated that 20% of depressive patients suffer from a thyroid dysfunction, mostly hypothyroidism.

Depression and Stroke

Depression is a common comorbidity in various somatic diseases such as cerebrovascular, cardiovascular and malig-

- umjereno tešku depresiju F32.1
- umjereno tešku depresiju sa somatskim simptomima F32.2
- tešku depresiju s psihotičnim simptomima F32.3

Kako prepoznati depresivni poremećaj

Depresivni poremećaji očituju se pojavom depresivnih epizoda koje obilježavaju različite kombinacije različitog broja od navedenih 9 (DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4. revizija)[3] ili 10 (MKB-10: International Classification of Diseases – 10. revizija)[4] simptoma. Da bi se mogla postaviti dijagnoza blage depresije potrebno je najmanje 4, za srednju 5 te za tešku 7 simptoma koji moraju postojati najmanje dva tjedna.

Tablica 1. Simptomi depresivne epizode prema MKB-10 i DSM-IV

MKB-10	DSM-IV
1. Depresivno raspoloženje (1)	Depresivno raspoloženje
2. Gubitak interesa i užitka	Smanjen interes i zadovoljstvo (2)
3. Smanjenje energije ili pojačano zamaranje	Umor ili gubitak energije skoro svaki dan (6)
4. Gubitak samopouzdanja i samopoštovanja	Osjećaj bezvrijednosti ili krivnje (7)
5. Neprimjereno samooptuživanje ili osjećaj krivnje	
6. Ponavljajuće misli o smrti ili samoubojstvu	Ponavljajuće misli o smrti ili samoubojstvu (9)
7. Otežano mišljenje i koncentracija; neodlučnost	Otežano mišljenje i koncentracija (8)
8. Agitacija ili retardacija	Agitacija ili retardacija skoro svaki dan (5)
9. Poremećaj spavanja	Insomnija ili hipersomnija (4)
10. Poremećaj apetita i promjena tjelesne tjelesne težine	Značajan gubitak ili po rast težine više od 5% (3)

U dijagnostičkom algoritmu svakako treba voditi računa o psihičkim i somatskim bolestima koje diferencijalno dijagnostički treba isključiti, npr. poremećaji štitnjače, Parkinsonova bolest, demencija i iscrpljenost prilagodbenih mogućnosti. Smatra se da oko 20 posto depresivnih bolesnika boluje od nekog poremećaja funkcije štitnjače, najčešće hipotireoze.

nant diseases, Parkinson's disease and chronic pain syndromes, which then additionally mask depression, hamper diagnosis and treatment, and further aggravate prognosis of both diseases. The rate of depression in particular somatic diseases is presented in Table 2.

Table 2. Somatic diseases and associated prevalence of depression

Somatic disease	Rate of depression (%)
Malignant disease	20-45
Stroke	26-34
Chronic pain syndromes	33-35
Cardiovascular diseases	15-33
Parkinson's disease	40

Cerebrovascular diseases, especially stroke, are characterized by an abrupt onset and severe disablement due to somatic symptoms such as motor, speech, swallowing, vision and hearing disturbances, central pain syndromes, etc. Such a sudden change of physical abilities is a major stress for every man, and for the majority of patients a traumatic experience they cannot sublimate but become disheartened, lose self-confidence, hope and life enthusiasm, which leads to depression, and considerably increases the risk of suicide and mortality in cerebrovascular patients. The clinical picture of depression frequently also includes somatic symptoms, headache and other pain syndromes, vertigo, nausea, loss of appetite and body weight, general physical fatigue and bed-ridden state, which are very similar to the symptoms of cerebrovascular diseases[5].

Also, a number of recent studies have shown that premorbid characteristics of mood disorder persisting for 10 to 15 years may significantly increase the risk of stroke. Somatic symptoms greatly hamper detection of depression in stroke patients. It is quite obvious that somatic disturbances and neuropathic central pain occurring in some 8% post-stroke patients will increase the risk of depression. On the other hand, functional disorders such as depression, anxiety and sleep disturbances are significantly associated as comorbidities with stroke and post-stroke pain syndrome, which should always be taken in consideration on differential diagnosis. The causal relationship between depression and stroke remain an area for additional research[6].

On differential diagnosis, the physician should differentiate depression occurring in response to traumatic stress caused by a severe somatic disease such as stroke in an intellectually preserved individual from the organic depressive disorder due to brain lesion. Such depression should be differentiated from the possible vascular dementia, Parkinson's disease and hypothyroidism.

Depresija i moždani udar

Depresija je čest pratilac različitih somatskih bolesti, kao što su cerebrovaskularne, kardiovaskularne, maligne, Parkinsonova bolest i kronični bolni sindromi, koje dodatno maskiraju depresiju, otežavaju dijagnostiku i liječenje te znatno pogoršavaju prognozu i jedne i druge bolesti. Učestalost pojave depresije uz pojedine tjelesne bolesti prikazana je u tablici 2.

Tablica 2. Tjelesne bolesti i učestalost javljanja depresije

Tjelesna bolest	Učestalost depresije (%)
Maligna bolest	20-45
Moždani udar	26-34
Kronični bolni sindromi	33-35
Kardiovaskularne bolesti	15-33
Parkinsonova bolest	40

Cerebrovaskularne bolesti, osobito moždani udar, nastaju naglo i često s teškim invaliditetom zbog somatskih simptoma kao što su poremećaj motorike, govora, gutanja, vida, sluha, centralnih bolnih sindroma i slično. Tako nagla promjena fizičkih sposobnosti za svakog čovjeka je intenzivan stres, a za velik dio bolesnika predstavlja traumatsko iskustvo koje nisu u stanju sublimirati nego postaju potišteni, gube samopouzdanje, nadu i volju za životom, što dovodi do depresije, znatno povećava rizik od samoubojstva i smrtnost cerebrovaskularnih bolesnika. Klinička slika depresije često uključuje i somatske simptome, glavobolju i druge bolne sindrome, vrtoglavicu, mučninu, gubitak apetita i tjelesne težine, opću tjelesnu slabost i zadržavanje u krevetu, vrlo slične simptomima cerebrovaskularnih bolesti[5].

Također, više studija u novije vrijeme pokazuje kako premorbidne osobine poremećaja raspoloženja kroz deset do petnaest godina mogu značajno povećati rizik za nastanak moždanog udara. Somatski simptomi značajno otežavaju otkrivanje depresije u cerebrovaskularnih bolesnika. Potpuno je jasno da će tjelesni poremećaji i neuropatska centralna bol koja nastaje nakon moždanog udara u oko 8 posto bolesnika povećati rizik nastanka depresije. S druge strane, funkcionalni poremećaji, kao što su depresija, anksioznost i poremećaj spavanja, značajno su komorbidno povezani sa cerebrovaskularnim inzultom i poslijeinzultnim bolnim sindromom, što diferencijalno dijagnostički uvijek treba uzeti u obzir. Utemeljenost uzročnoposljedične povezanosti između depresije i moždanog udara ostaje kao važno područje za daljnja istraživanja[6].

Risk Factors Linking Depression and Cerebrovascular Disease

Depression frequently occurs consequentially to stroke, however, the premorbid mood disorder and depression as a risk factor for cerebrovascular disease should not be neglected either. Depression and stroke show a significant causal relationship through their common risk factors of stress, inadequate physical activity, loss of energy, alcohol abuse and alcoholism, tobacco smoking, coagulation and heart rate impairments, hypertension, cardiac infarction, and type 2 diabetes[1,7,8]. The following risk factors are most commonly related to the occurrence of post-stroke depression: a history of depression, a history of other mental disorders, post-stroke feeling of loneliness and social isolation, dysphasia and functional impairments, central pain syndromes, advanced age, low socioeconomic status, previous social problems, reduced daily activities, and reduced sexual performance[1,9].

Treatment

Attempts have been made to prevent depressive mood and development of major depression in stroke patients by psychotherapy and psychopharmacotherapy in order to improve their physical and mental state. Psychotherapy definitely has a favorable effect mood improvement, however, there is no efficient method to prevent depression in stroke patients.

Proper understanding of the psychodynamics of the relationship between cerebrovascular disease and depression, explained through frequent psychotherapeutic conversation between the physician and the patient, is highly relevant for therapeutic outcome. The most efficient treatment of depression and stroke comorbidity includes a combination of brief psychotherapeutic procedures such as behavioral, cognitive-behavioral and interpersonal psychotherapy with psychopharmaceuticals, primarily SIPPS class antidepressants[1,5,6].

- The aim of cognitive-behavioral psychotherapy is to make the patient aware of the character, course and prognosis of the disease, and to instruct him on the best methods of treatment, at the same time stimulating him for additional efforts in ever greater use of the residual psychophysical abilities.
- Interpersonal psychotherapy administered for 12-16 weeks is aimed at detecting the patient's interpersonal problems and improving his ability for interpersonal communication. Antidepressants are frequently added to psychotherapy.

Diferencijalno dijagnostički liječnik treba razlikovati depresiju koja se javi kao reakcija na traumatski stres uzrokovan teškom tjelesnom bolešću kao što je moždani udar u intelektualno očuvane osobe od organskog depresivnog poremećaja koji je posljedica oštećenja mozga. Također depresiju treba razlikovati od moguće vaskularne demencije, Parkinsonove bolesti i hipotireoze.

Rizični čimbenici povezuju depresiju i cerebrovaskularnu bolest

Depresija se javlja često kao posljedica moždanog udara, a ne treba zanemariti premorbidni poremećaj raspoloženja i depresiju kao čimbenik rizika za nastanak cerebrovaskularne bolesti. Depresija i moždani udar značajno su uzročno povezani zajedničkim rizičnim čimbenicima: stresom, smanjenjem fizičke aktivnosti, gubitkom energije, zlouporabom alkohola i alkoholizmom, pušenjem duhana, poremećajem koagulacije i srčanog ritma, hipertenzijom, srčanim infarktom i šećernom bolešću tipa 2[1,7,8]. S nastankom poslijeinzultne depresije najviše se povezuju slijedeći rizični čimbenici: anamneza depresije, anamneza drugih psihičkih poremećaja, usamljenost i socijalna izolacija poslije moždanog udara, disfazija i funkcionalna oštećenja, centralni bolni sindromi, starija dob, slabiji socioekonomski status, prijašnji socijalni problemi, smanjene aktivnosti tijekom dana i smanjenje seksualnih sposobnosti[1,9].

Liječenje

Postoje pokušaji da se psihoterapijom i psihofarmakoterapijom spriječi depresivno raspoloženje i razvoj velikog depresivnog poremećaja kod bolesnika s moždanim udarom i na taj način poboljša njihovo tjelesno i psihičko stanje. Psihoterapija svakako ima pozitivan učinak na poboljšanje raspoloženja, no zasad nema učinkovite metode sprječavanja depresivne bolesti u bolesnika koji su doživjeli moždani udar.

Za ishod liječenja značajno je razumijevanje psihodinamike odnosa cerebrovaskularne bolesti i depresije, koja se razjašnjava kroz česte psihoterapijske razgovore između liječnika i bolesnika. Najdjelotvornije liječenje depresije u komorbiditetu s moždanim udarom je ono pomoću kombiniranih kratkih psihoterapijskih postupaka kao što su bihevioralna, kognitivno-bihevioralna i interpersonalna psihoterapija uz pomoć psihofarmaka, prvenstveno antidepresiva iz skupine SIPPS[1,5,6].

- Kognitivno-bihevioralna psihoterapija treba bolesniku osigurati spoznaju o naravi, tijeku i prognozi bolesti te upute o najboljim metodama liječenja uz poticaj za

- Besides their antidepressive and anxiolytic action, antidepressants, selective inhibitors of serotonin reuptake (SIPPS) also act on the platelet membrane serotonin carrier, thus reducing the platelet serotonin level and platelet coagulability, and have a heart rate and blood pressure regulating activity mediated by the central nervous system.
- Electroconvulsive therapy (ECT) is used in cases resistant to psychotherapy and psychopharmacotherapy, and when a rapid antidepressive effect has to be achieved.

Conclusions

1. Cerebrovascular diseases currently present a leading health problem in western countries, and depression is the fourth health problem worldwide.
2. Today, the association between depression and stroke is considered unquestionable.
3. Depression is the most common psychiatric disorder associated with cerebrovascular diseases; it occurs in 26% to 34% of stroke patients within two years of stroke.
4. There is a correlation between the severity of post-stroke depression and cerebral lesion localization, i.e. the closer the brain lesion to the left frontal lobe region, the higher the prevalence and severity of depression.
5. Early detection and treatment have been defined as the main goals of modern medicine.
6. Attempts at preventing post-stroke depression have been less successful.
7. The treatment is successfully performed by use of psychotherapy, psychopharmacotherapy, electroconvulsive therapy, and rehabilitation.
8. The biopsychological model provides proper understanding of the multifactorial etiology of mental and physical disturbances of post-stroke depression, which is a precondition for a comprehensive, team-based treatment.

Questions

1. Depression is:
   - fourth major health problem in western countries
   - mood disorder
   - clinical picture characterized by mental and physical symptoms
   - most common mental disorder associated with stroke
   - all of these

dodatno unapređivanje i uporabu preostalih psihofizičkih sposobnosti.

- Interpersonalna psihoterapija u trajanju od 12 do 16 tjedana usmjerana je na otkrivanje bolesnikovih međuljudskih problema i poboljšanje sposobnosti međuljudskih komunikacija. Antidepresivi se često pridodaju uz psihoterapiju.
- Uz njihovo antidepresivno i anksiolitično djelovanje, antidepresivi, selektivni inhibitori ponovne pohrane serotonina (SIPPS) utječu na trombocitni membranski nosač serotonina tako da smanjuju količinu serotonina u trombocitima i njihovu koagulabilnost, a posredstvom središnjeg živčanog sustava reguliraju srčani ritam i krvni tlak.
- Elektrokonvulzivna terapija (EKT) se primjenjuje u slučajevima otpornim na psihoterapiju i psihofarmakoterapiju te kada je potrebno postići brz antidepresivni učinak.

Zaključci

1. Cerebrovaskularne bolesti predstavljaju danas vodeći zdravstveni problem u zemljama zapadnog svijeta, a depresija je četvrti najveći zdravstveni problem.
2. Danas se smatra da je povezanost između depresije i moždanog udara nedvojbena.
3. Depresija je najčešći psihijatrijski poremećaj povezan s cerebrovaskularnim bolestima, javlja se u 26 do 34 posto bolesnika unutar dvije godine poslije moždanog udara.
4. Postoji povezanost između težine poslijeinzultne depresije i lokacije lezije mozga: što su oštećenja mozga bliže području lijevog frontalnog režnja, učestalost i težina depresije je veća.
5. Rano otkrivanje i liječenje postaje jedan od temeljnih ciljeva suvremene medicine.
6. Pokušaji sprječavanja poslijeinzultne depresije dosad su bili manje uspješni.
7. Liječenje se uspješno provodi primjenom psihoterapije, psihofarmakoteraije, elektrokonvulzivne terapije i rehabilitacije.
8. Biopsihološki model omogućuje razumijevanje višečimbenske etiologije psihičkih i fizičkih poremećaja poslijeinzultne depresije kao preduvjeta za sveobuhvatno, timsko uspješno liječenje.

2. Post-stroke depression occurs in:
   - 10% of patients
   - 15%-20% of patients
   - 26%-34% of patients
   - 35%-40% of patients
   - 50% of patients
3. Depression is treated by:
   - antidepressants
   - anxiolytics
   - psychotherapy
   - antipsychotics
   - psychotherapy and antidepressants
4. Symptoms of depression are:
   - depressive mood
   - loss of interest
   - decreased energy and increased fatigue
   - sleep disturbances
   - all of these
5. Post-stroke depression most commonly occurs in the lesion of:
   - left frontal lobe
   - left temporal lobe
   - right occipital lobe
   - right parietal lobe
   - left parietal lobe

Pitanja

1. Depresija je:
   - četvrti najveći zdravstveni problem zemalja zapadnog svijeta
   - poremećaj raspoloženja
   - klinička slika se očituje psihičkim i fizičkim simptomima
   - najčešći psihički poremećaj povezan s moždanim udarom
   - sve od navedenog
2. Poslijeinzultna depresija javlja se:
   - 10% bolesnika
   - 15-20% bolesnika
   - 26-34% bolesnika
   - 35-40% bolesnika
   - 50% bolesnika
3. Depresija se liječi:
   - antidepresivima
   - anksioliticima
   - psihoterapijom
   - antipsihoticima
   - psihoterapijom i antidepresivima
4. Simptomi depresije su:
   - depresivno raspoloženje
   - gubitak interesa
   - smanjenje energije i povećano zamaranje
   - poremećaj spavanja
   - sve navedeno
5. Poslijeinzultna depresija najčešće se javlja kod oštećenja:
   - lijevog frontalnog režnja
   - lijevog temporalnog režnja
   - desnog okcipitalnog režnja
   - desnog parietalnog režnja
   - lijevog parietalnog režnja

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NEW OPTIONS IN NEUROREHABILITATION
NOVE MOGUĆNOSTI U NEUROREHABILITACIJI

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About 20% of stroke patients die within a month of stroke onset, whereas another 30% are dependent on other people's help, 25% continue treatment and care at specialized institutions, and 10% are bed ridden. Post-stroke rehabilitation should be initiated as early as possible, it means, immediately when a stable medical condition is achieved, and preferably at stroke units. Early rehabilitation should be initiated by an interdisciplinary approach at stroke units that are structured so as to allow for at least weekly staff meetings and patient rehabilitation of at least 3 hours daily. A well coordinated team work of the specialist physician, patient and his patient family has been shown to be crucial for successful rehabilitation.

Until recently, the concepts of the pathophysiology of post-stroke rehabilitation considered training patients in new, compensating techniques (e.g., use of unaffected arm in achieving independence) and avoiding intensive therapy of the affected extremity as a favorable effect of rehabilitation.

Current concepts, however, indicate that a favorable effect of rehabilitation can be achieved by repeated patient participation in active physical therapy program, thus directly addressing the process of functional reorganization in the brain and neurologic improvement.

Nowadays, there are two main theories on post-stroke recovery: theory of collateral branching from intact cells into denervated area, and theory of demasking the neural pathways and synapses otherwise used that can be included upon the dominant system breakdown.

It is believed that there are two mechanisms of neurologic function recovery:

1) cessation of the adverse effect of local factors (resolution of local edema, resorption of local toxins, improvement of local circulation, recovery of neurons partially damaged by ischemia), leading to early spontaneous recovery within 3-6 months of stroke; and
2) the principle of brain neuroplasticity, i.e. the nervous system ability to modify structures and functional or-

Unutar mjesec dana od nastanka moždanog udara umire 20% bolesnika, dok ih 30% postaje ovisno o tuđoj pomoći, 25% ih nastavlja liječenje i njegu u specijaliziranim ustanovama, a 10% bolesnika ostaje vezano uz krevet. Rehabilitaciju bolesnika nakon moždanog udara treba započeti što ranije, točnije odmah, u jedinicama za liječenje moždanog udara kada je bolesnik u medicinski stabilnom stanju. Ranu rehabilitaciju treba započeti interdisciplinski u jedinici za liječenje moždanog udara koja po svojoj organizaciji omogućuje sastanke osoblja barem jedanput na tjedan, a rehabilitaciju u trajanju od barem tri sata na dan.

Pokazalo se je da je ključ uspješne rehabilitacije u usklađenom timskom radu specijalista liječnika, bolesnika i njegove obitelji.

Prema dosadašnjem poznavanju patofiziologije oporavka od moždanog udara pozitivnim učinkom rehabilitacije smatralo se je učenje bolesnika novim kompenzirajućim tehnikama (npr. uporaba nezahvaćene ruke u postizanju neovisnosti) te izbjegavanje intezivne terapije oslabljenog ekstremiteta. Današnje spoznaje nam govore kako se pozitivan učinak rehabilitacije postiže opetovanim sudjelovanjem bolesnika u aktivnom programu fizikalne terapije, čime se postiže izravan utjecaj na proces funkcionalne reorganizacije u mozgu i poboljšanje neurološkog oporavka.

Danas postoje dvije glavne teorije oporavka nakon moždanog udara: teorija o kolateralnom grananju iz intaktnih stanica u denervirano područje i teorija o demaskiranju neuralnih putova i sinapsa koje se inače rabe, a koje se mogu uključiti nakon sloma dominantnog sustava.

Smatra se kako postoje dva mehanizma oporavka neurološke funkcije:

1. Prestanak štetnog učinka lokalnih čimbenika (rezolucija lokalnog edema, resorpcija lokalnih toksina, poboljšanje lokalne cirkulacije, oporavak ishemijom djelomice oštećenih neurona), koji dovodi do ranog spontanog oporavka nakon moždanog udara unutar prvih 3 do 6 mjeseci.

ganization, based on collateral expansion of new synaptic links and demasking of latent functional pathways by taking functions over through alternative neural pathways, diaschisis reversibility, denervation supersensitivity and regenerative proximal expansion of interrupted axons.

The polypeptide growth factors (basic fibroblast growth factor, bFGF) stimulating neuronal branching and endogenous proliferation of progenitor cells in experimental animals, may also play a role in the post-stroke functional recovery, whereas bFGF dimer has been shown to improve neurologic recovery in subacute treatment (days, weeks).

Medications that modify the level of specific central neurotransmitters were experimentally demonstrated to influence post-stroke functional recovery of the brain. The substances that decrease the concentration of norepinephrine (a_1-adrenergic receptor blockers, a_2-adrenergic receptor agonists) reduce post-stroke recovery, whereas those increasing the concentration of norepinephrine (a_2-adrenergic receptor antagonists, sympatomimetics, e.g., amphetamine) improve post-stroke recovery.

Classic rehabilitation services are categorized into physical therapy, work therapy and speech therapy. Physical therapy is based on specific functional training performed through traditional therapeutic techniques (extent of movement, musculature strengthening, mobilization, technique mastering), using methods according to Knott and Voss (proprioceptive neuromuscular facilitation), Brunnstrom (stimulating specific synergy by use of cutaneous/proprioceptive central facilitation) and Bobath (training of neural development). Physical and work therapy are based on the substitutional action of unaffected parts of the body and biologic principles of brain plasticity. Forced movement induction stimulates enhanced functioning of the unaffected hemisphere relative to the affected part of the body, and forced directing patient's attention to the paretic extremity through high-intensity functional training results in better recovery.

Unfortunately, the process of rehabilitation seems to terminate with the patient's stay at special institutions. However, there is now an alternative to classic rehabilitation, i.e. tele-rehabilitation or computer aided rehabilitation and care.

The idea of treating patients with aphasia by use of computer has been launched some ten years ago. The latest approach to this mode of treatment implies so-called face-to-face therapy, i.e. the patient presenting to a special institution immediately upon the onset of stroke symp-

2. Načelo neuroplastičnosti mozga, odnosno sposobnosti živčanog sustava za modificiranje strukture i funkcionalne organizacije, koje se temelji na kolateralnom širenju novih sinaptičnih veza i na demaskiranju latentnih funkcionalnih putova, preuzimanju funkcije kroz alternativne neuralne putova, reverzibilnosti dijashize, denervacijskoj superosjetljivosti i regenerativnom proksimalnom širenju prekinutih aksona.

Moguću ulogu u funkcionalnom oporavku nakon ishemijskog moždanog udara imaju i polipeptidni faktori rasta (*basic fibroblast growth factors*, bFGF) koji potiču grananje neurona i endogenu poliferaciju progenitornih stanica kod pokusnih životinja, a pokazalo se je da dimer bFGF u subakutnom liječenju (dani, tjedni) poboljšava neurološki oporavak.

U eksperimentalnim uvjetima dokazano je kako lijekovi koji mijenjaju razinu specifičnih središnjih neurotransmitora utječu na oporavak funkcije mozga nakon moždanog udara. Tvari koje smanjuju koncentraciju norepinefrina (blokatori alfa 1-adrenergičnih receptora, agonisti alfa 2-adrenergičkih receptora) smanjuju oporavak, a tvari koje povisuju koncentraciju norepinefrina (antagonisti alfa 2-adrenergičnih receptora, simpatomimetici kao amfetamin) poboljšavaju oporavak nakon moždanog udara.

Klasične rehabilitacijske službe dijele se na fizikalnu terapiju, radnu terapiju i terapiju govora. Fizikalna terapija osniva se na specifičnom funkcionalnom vježbanju, a provodi se putem tradicionalne terapije (opseg pokreta, jačanje muskulature, mobilizacija, usvajanje tehnike), metodom Knotta i Vossa (proprioceptivna neuromuskularna facilitacija), Brunnstroma (poticanje specifične sinergije uporabom kutano/proprioceptivne centralne facilitacije) i Bobatha (trening neuralnog razvoja). Fizikalna i radna terapija zasnivaju se na supstitucijskom radu nezahvaćenih dijelova tijela i biološkim načelima plastičnosti mozga. Prisilnim izazivanjem kretnja postiže se pojačano funkcioniranje neoštećene hemisfere u odnosu na oslabljeni dio tijela, a "forsiranom uporabom" i usmjeravanjem bolesnikove pozornosti na paretični ekstremitet funkcionalnim treningom visokog inteziteta postiže se bolji oporavak.

Čini se da nakon boravka u specijaliziranim ustanovama rehabilitacija bolesnika, nažalost, završava. Međutim, danas postoji i alternativa klasičnoj rehabilitaciji, kao što je tele-rehabilitacija, rehabilitacija i liječenje uz pomoć računala. Zamisao o liječenju bolesnika s afazijom pomoću računala stara je već dvadesetak godina. Najnoviji pristup takovom liječenju predstavlja tzv. "terapija licem u lice", koja pretpostavlja dolazak bolesnika u specijaliziranu

toms, making the diagnosis of aphasia, initiating face-to-face therapy and combining classic therapy for aphasia with computer aided therapy at patient's home. Thus, the speech therapist can evaluate therapeutic results immediately upon therapy completion, assess therapeutic progress and plan further treatment by use of data transfer. This therapy is preferable for higher patient motivation and self-confidence and absence of age restrictions, however, its shortcomings are the fact that stroke patients suffer from depressed cognitive abilities and a limited number of exercises provided with respective software for the treatment of aphasia.

By use of so-called virtual reality, i.e. computer simulation producing an impression of real 3D environment, intensified learning of the mechanisms is achieved by sending information on patient's movements to the central nervous system in real time *via* audio-visual feedback connection, thus allowing for individual adjustment of the rehabilitation therapy intensity. The use of virtual reality in neurologic patients is based on three main points:

1) applicability, by use of a 'helmet' attached to the head (visual image, earphones and 3D position sensor), preventing the patient's attention to decrease, and virtual environment projected to the wall in a pleasant, dark room for motor rehabilitation;
2) patient's utilizing the mechanism of 'enhanced learning' by use of information sent to the central nervous system in real time, acquired *via* audio-visual feedback connection for movements that interact with correct movements presented in virtual environment; and
3) extrapolation of the movements learned through virtual reality to the real life, thus achieving considerable improvement in the results of extremity motor functions on clinical evaluation scales in post-stroke patients; the intensity of rehabilitation exercise can be increased or otherwise adjusted to each individual patient.

Tele-rehabilitation programs *via* regular telephone or special digital connection increase the availability of special rehabilitation service to patients, caretakers and students in remote and rural areas; it also allows for audio-visual link between patients and their tele-therapists, and there is no 'idling' in the process of rehabilitation due to temporal, spatial, geographical or communication distance.

ustanovu odmah nakon nastanka simptoma moždanog udara, dijagnosticiranje afazije i početak terapije "licem u lice", te kombiniranje klasične terapije afazije s terapijom uz pomoć računala u bolesnikovu domu. Takovom terapijom logoped ocjenjuje rezultat terapije odmah nakon njezinog završetka i procjenjuje napredak liječenja te planira daljnje liječenje putem prenošenja podataka. Prednosti takve terapije su veća motiviranost i samopouzdanje bolesnika te nepostojanje dobne granice za provođenje terapije, a ograničenja su činjenica da je kod bolesnika s moždanim udarom smanjena kognitivna sposobnost i ograničen broj vježba s postojećim računalnim programom za liječenje afazije.

Pomoću takozvane "virtualne stvarnosti", odnosno računalne simulacije koja stvara dojam stvarnog 3D okruženja postiže se "pojačano učenje" mehanizama slanjem informacija središnjem živčanom sustavu u stvarnom vremenu preko audio-vizualne povratne veze o bolesnikovim pokretima i postiže se mogućnost individualnog prilagođavanja intenziteta rehabilitacijske terapije. Tri su temeljne točke u primjeni virtualne stvarnosti kod neuroloških bolesnika:

1. Uporabljivost, pomoću "kape" koja se pričvrsti na glavu (vizualni prikaz, slušalice i 3D položajni senzori), čime se onemogućuje bolesnikovo opadanje pozornosti, te s virtualnim okruženjem projiciranim na zidu ugodne, tamne prostorije za motornu rehabilitaciju.
2. Bolesnikova uporaba mehanizma "pojačanog učenja" korištenjem informacija upućenih središnjem živčanom sustavu u stvarnom vremenu, dobivenih preko audio-vizualne povratne veze svojih kretnja, koje su u interakciji s pravilnim kretnjama prikazanim u virtualnom okruženju.
3. Prijenos naučenih kretnja putem virtualne stvarnosti u stvaran život, čime se postiže značajan porast rezultata motornih funkcija ekstremiteta na kliničkim ocjenskim ljestvicama kod bolesnika nakon moždanog udara i mogućnost povećanja intenziteta rehabilitacijskih vježba i prilagodbe svakom pojedinom bolesniku.

Tele-rehabilitacijskim programima putem redovne telefonske linije ili specijaliziranih digitalnih veza postiže se bolja dostupnost specijaliziranih rehabilitacijskih usluga bolesnicima, njegovateljima i studentima u udaljenim i seoskim područjima; omogućuje se bolesnicima i njihovim tele-terapeutima audiovizualna povezanost; i nema "praznog hoda" u procesu rehabilitacije uzrokovanog vremenskom, zemljopisnom ili prometnom udaljenošću.

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CURRENT METHODS IN THE MANAGEMENT OF NICOTINE ADDICTION IN PATIENTS WITH CEREBROVASCULAR DISORDERS

SUVREMENE METODE LIJEČENJA OVISNOSTI O NIKOTINU KOD BOLESNIKA S POREMEĆAJIMA MOŽDANE CIRKULACIJE

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Dependence on any drug including nicotine is basically a cerebral disorder. Neurobiologic investigations suggest a qualitative difference between the brain of an addict and the brain of a person free from any addiction. On the other hand, behavioral science points out that the brain of an addict is abnormally conditioned, so that some environmental factors become substantial elements of addiction and dependent behavior. One of the specificities of cigarette smoking relative to other dependences is that in addition to nicotine, which is extremely addictive, a smoker on inhaling tobacco smoke on twenty or more occasions daily at the same time not only strengthens his nicotine dependence but also takes more than 4000 adverse chemical substances, among them about 50 carcinogens.

Cigarette smoking has been associated with at least 30 different diseases that rank high on the morbidity and mortality scale, among the stroke. Stroke is more frequent in smokers than in nonsmokers. It should be noted that there is no healthy level of tobacco smoking, because nicotine, carbon monoxide, carcinogenic substances and thousands of other harmful chemicals are taken to the body while inhaling the smoke of each cigarette. Each cigarette impairs breathing, paralyzes ciliary apparatus, deprives the body of oxygen, narrows blood vessels, accelerates heart

Ovisnost o bilo kojoj drogi, pa tako i o nikotinu, u osnovi je bolest mozga. Neurobiološka ispitivanja govore u prilog kvalitativne razlike između mozga ovisnika i mozga osobe koja nije ovisnik. S druge strane bihevioralna znanost ističe da je mozak ovisnika nenormalno kondicioniran, tako da neki čimbenici okoline postaju bitni dijelovi ovisnosti, odnosno ovisničkog ponašanja. Jedna od specifičnosti pušenja u odnosu na druge ovisnosti je u tome što pušač uz nikotin, koji je izrazito adiktivan, udisanjem duhanskog dima dvadesetak i više puta na dan istodobno ne samo učvršćuje svoju ovisnost o nikotinu, već unosi u tijelo preko četiri tisuće štetnih kemijskih sastojaka među kojima je oko pedeset kancerogena.

Pušenje se povezuje s najmanje tridesetak različitih bolesti visoko stupnjevanih na ljestvici pobola i smrtnosti, među kojima je i moždani udar. Moždani udar se kod pušača javlja češće i ranije nego u nepušača. Treba istaknuti da ne postoji zdrava razina pušenja duhana, jer se udisanjem dima svake cigarete u tijelo unosi nikotin, ugljični monoksid, kancerogene tvari i tisuće drugih štetnih kemikalija. Svaka cigareta remeti disanje, paralizira cilijarni aparat, oduzima tijelu kisik, sužava krvne žile, ubrzava rad srca i podiže krvni tlak, djeluje bifazično na središnji živčani sustav, šteti zdravlju osobe koja je uz pušača i vodi prema

rate and elevates blood pressure, acts biphasically on the central nervous system, has detrimental health effects for the persons close to the smoker, and leads to addiction. Disability and deaths related to smoking are not unavoidable but preventable. With the elimination of smoking as a risk factor, not only a lower number of strokes but also a higher proportion of patients with good recovery can be expected.

Current methods in the management of nicotine dependence include a combination of behavioral and cognitive therapy with adjuvant pharmacologic agents (nicotine replacement therapy, bupropion as the first non-nicotine adjuvant in the process of cessation).

Each smoker can quit smoking irrespective of the duration of smoking habit and number of cigarettes smoked. Also, each smoker has the right to get support and assistance in the process of cessation, which consists of a number of steps. This especially holds for smokers who have experienced a stroke or heart attack, because successful treatment and rehabiliation are incompatible with continuing smoking.

As smoking is a very complex addiction, most patients-smokers manage to abstain for a short period of time when symptoms of the disease occur, whereafter they turn back to cigarettes. Many of them report on finding themselves in a sort of a "vicious circle", being through a stage of considering the need of quitting, stage of taking some concrete steps, stage of brief cessation, then turning back to smoking.

The smoking cessation programs should be incorporated in the regular outpatient, hospital and post-hospital therapeutic procedures in outpatient clinics and at particular hospital departments where smoking related diseases are treated. High risk patients with a history of numerous attempts at quitting smoking and low level of self-confidence because of repeated failures require special support and help to allow them not only to become but also to stay nonsmokers.

Smokers try to stop smoking in a number of different ways. Irrespective of the method they choose, it should be noted that there is no magic formula to transform a smoker into a nonsmoker. Smoking cessation is not an event but a process during the course of which the smoker approaches his goal step by step. Mental cessation persists for a long time after the smoker had his last cigarette. In this long-term process it is of utmost importance to focus on the multiple benefits and gains in terms of improving and protecting both one's health and money. In only 24 hours of abstinence, the risk of sudden death from infarction is

ovisnosti. Invaliditet i smrti vezane uz pušenje nisu neizbježne, nego ih je moguće spriječiti. Uklanjanjem pušenja kao rizičnog čimbenika može se očekivati ne samo manji broj moždanih udara, nego i veći postotak bolesnika s dobrim oporavkom.

Suvremene metode liječenja ovisnosti o nikotinu uključuju kombinaciju bihevioralne i kognitivne strategije s pomoćnim farmakološkim sredstvima (nikotinska zamjenska terapija, bupropion kao prvo nenikotinsko pomoćno sredstvo u procesu odvikavanja od pušenja).

Bez obzira na dužinu pušačkog staža i broj popušenih cigareta svaki pušač može prestati pušiti. Uz to, svaki pušač ima pravo dobiti potporu i pomoć u procesu odvikavanja od pušenja koji se sastoji od više faza. To se osobito odnosi na pušače oboljele od moždanog ili srčanog udara, jer su uspješno liječenje i rehabilitacija nespojivi s nastavkom pušenja.

Kako se radi o vrlo složenoj ovisnosti, većina bolesnika pušača uspijeva apstinirati kratko vrijeme kad se jave simptomi bolesti, nakon čega se vraćaju cigareti. Iskustvo mnogih je da se dugo vremena vrte u začaranom krugu prolazeći kroz faze razmišljanja o potrebi prestanka pušenja, faze poduzimanja određenih konkretnih koraka, faze kraćeg prestanka i nakon toga ponovnog vraćanja pušenju.

Programe odvikavanja od pušenja stoga treba uklopiti u redovite ambulantne, bolničke i poslijebolničke terapijske postupke u ambulantama i na pojedinim klinikama gdje se liječe bolesti povezane s pušenjem. Visokorizičnim bolesnicima s brojnim pokušajima prestanka pušenja i niskom razinom samopouzdanja zbog opetovanih neuspjeha potrebna je posebna potpora i pomoć kako bi im se omogućilo ne samo da postanu, nego i da ostanu nepušači.

Pušači na razne načine pokušavaju prestati pušiti. Bez obzira na to za koju metodu se odluče treba istaknuti kako ne postoji magična formula kojom bi se pušača moglo pretvoriti u nepušača. Prestanak pušenja nije događaj nego proces tijekom kojega se pušač korak po korak približava cilju. Mentalno odvikavanje od pušenja traje još dugo vremena nakon što je pušač zapalio zadnju cigaretu. U cijelom tom procesu bitno je usredotočiti se na višestruke prednosti i dobiti u vidu poboljšanja i čuvanja zdravlja i novaca. Već nakon prva 24 sata apstinencije smanjuje se rizik iznenadne smrti zbog infarkta, snižava se razina CO u krvi, više kisika dolazi u mozak i druge organe, krvni tlak se spušta, a rad srca se normalizira. Nakon nekoliko dana okus i miris se popravljaju, šetnja je manje naporna, disanje je lakše, dah više nije tako kratak i povećava se osjećaj snage.

Liječnici i ostali medicinski djelatnici koji sudjeluju u dijagnostičkim i terapijskim postupcima mogu kratkom

reduced, the blood level of CO is lowered, the oxygen supply to the brain and other organs increase, blood pressure declines and heart rate shows normalization. After several days of abstinence, the sense of taste and smell improves, the walk is better tolerated, the breathing is easier, the breath is not short anymore, and the feeling of strength improves.

Physicians and other medical personnel involved in diagnostic and therapeutic procedures can help the patient by brief intervention in the process of smoking cessation. ***Brief intervention*** means that each patient should be asked about smoking, and if a smoker he should be advised to stop smoking, to assess whether he is willing to do it immediately or within a one-month period, to help him set a date for cessation and advise him how to successfully cope with withdrawal discomforts, and to follow-up the course of abstinence at an intensive rate for the first two weeks, then less frequently, once a week for one month, and then monthly for one year.

5 A	Ask	Assess	Attend
	Advise	Assist	

Using ***motivating interview*** the patient can be attracted to decide, if he has not yet done so, to stop smoking, for his own reasons rather than for some general facts about the detrimental effects of cigarette smoking.

What do you like in smoking?
What do you dislike in smoking?
Where are you in this relationship of love and hate for smoking?

It is crucial to make a good plan. Motivation is of paramount importance, because the stronger the motivation the greater the chance for success. Upon setting a date for quitting smoking, which should not be to distant, an appropriate support from the family and friends as well as professional help should be ensured. During the development of nicotine addiction, smokers at first fool themselves thinking they can simply stop smoking whenever they want to, however, the true is far from this. Most smokers wish to stop smoking, one third try to stop at least once a year, but only five percent of them manage to abstain by the end of the one-year period.

Nicotine dependence test

How many cigarettes do you smoke daily?
How much time usually elapses between your standing up until your first cigarette?

intervencijom pomoći bolesniku u procesu prestanka pušenja. ***Kratka intervencija*** sastoji se u tome da se svakog bolesnika obvezno pita puši li, da mu se savjetuje prestanak pušenja, da se procjeni je li voljan to učiniti odmah ili unutar mjesec dana, da mu se pomogne odrediti datum prestanka pušenja i kako se uspješno suočiti s apstinencijskim poteškoćama, te da se prati tijek apstinencije intenzivno kroz prva dva tjedna, a zatim rjeđe, jedanput na tjedan kroz mjesec dana, potom svakog mjeseca kroz godinu dana.

5 P	Pitati	Procijeniti	Pratiti
	Posavjetovati	Pomoći	

Pomoću ***motivirajućeg razgovora*** bolesnika se može zainteresirati da, ako još nije, donese odluku o prestanku pušenja utemeljenu na osobnim razlozima, a ne zbog nekih općih činjenica o štetnosti pušenja.

Što Vam se sviđa u pušenju?
Što ne volite kod pušenja?
Gdje ste Vi u tom odnosu ljubavi i mržnje prema pušenju?

Svakako je ključno načiniti dobar plan. Motivacija je jako važna, jer što je ona veća to je veća i mogućnost uspjeha. Nakon određivanja datuma prestanka pušenja koji ne bi trebao biti predalek, važno je osigurati odgovarajuću potporu prijatelja i obitelji te stručnu pomoć. Tijekom razvoja ovisnosti o nikotinu pušači se isprva zavaravaju mišlju kako mogu jednostavno, kadgod zažele, prestati pušiti. Stvarnost je drukčija. Većina pušača želi prestati, trećina barem jedanput na godinu pokušava ostaviti cigarete, a svega ih pet posto uspijeva apstinirati do kraja godine.

Test ovisnosti o nikotinu

Koliko cigareta pušite na dan?
Koliko vremena prođe ujutro nakon ustajanja do paljenja prve cigarete?
Je li Vam teško izdržati bez cigarete na mjestima gdje pušenje nije dopušteno ili u prilikama kad to nije primjereno?

Onaj tko puši najmanje deset cigareta na dan prvu cigaretu zapali tijekom trideset minuta nakon buđenja ujutro, jer osjeća nelagodu ako to ne učini i teško mu je izdržati u prigodama gdje se ne smije pušiti i jedva čeka priliku da zapali cigaretu s velikom vjerojatnošću je razvio ovisnost o nikotinu.

Pušači godinama učvršćuju složenu pušačku naviku. Kupovanje cigareta, otvaranje kutije, vađenje cigarete, prinošenje ustima, paljenje, stavljanje i vađenje cigarete iz usta nekoliko stotina puta na dan, gašenje i odlaganje opušaka

Is it hard for you to abstain from smoking at places where smoking is forbidden or in some situations when it would not be appropriate?

Those smoking at least ten cigarettes daily and have their first cigarette some 30 minutes of waking up in the morning because they do not feel comfortable unless they do it, and those who can hardly stand situations where smoking is inappropriate and cannot wait to have a cigarette, have probably developed nicotine dependence.

Smokers fix their complex smoking habit for years. Buying cigarettes, opening the pack, taking the cigarette out of the pack and lighting it, taking it to and from the mouth hundreds of times daily, stubbing it out, and disposing butts becomes a routine. On solving daily problems and stresses, a smoker will light a cigarette and feel comfortable due to the nicotine activation of the dopaminergic system. He cannot imagine living without cigarettes, which uses like a sort of "crutches" to rely on when tired or oppressed with problems. In case of cigarette shortage and nicotine level decline, unpleasant withdrawal symptoms occur such as desire for cigarette, irritability, frustration or anger, anxiety, concentration difficulties, fatigue, increased appetite, retarded heart rate, etc., which disappear as soon as he lights a cigarette and meets the nicotine requirement. Therefore it is no surprise that relapses are quite usual in most smokers and are considered a normal part of the process of smoking cessation. A smoker using a pack of cigarettes *per* day inhales nicotine 160 times every day (on smoking one cigarette, tobacco smoke is inhaled about eight times), which means that he supports and reinforces his nicotine dependence 57,400 times a year.

At University Department of Neurology, Sestre milosrdnice University Hospital, the so-called brief intervention has been used and special programs are organized for smokers with high-grade dependence for whom the former is inadequate. The program of smoking cessation is based on the "Breathe free plan to stop smoking" principles of the American authors Folkenberg and McFarland. This is a psychotherapeutic-educational model. In some smokers, the ***nicotine replacement therapy***, mostly in the form of adhesive strip, has been used to alleviate withdrawal symptoms. With the use of nicotine adhesive strips, the blood level of nicotine is lower than with cigarette smoking but yet high enough to alleviate or eliminate the nicotine withdrawal syndrome and to facilitate cessation. In addition, all harmful constituents taken on cigarette smoking are removed from the strips. Strips are applied on intact, hairless skin and daily exchanged. There are strips with a variable amount of nicotine (21 mg, 14 mg, 7 mg). The 21-

postaje rutina. Pri rješavanju svakodnevnih problema i stresova pušač obvezno pali cigaretu i doživljava ugodu vezano uz aktiviranje dopaminergičnog sustava nikotinom. Ne može zamisliti život bez cigarete koju rabi poput štake za oslonac kad mu je teško. U slučaju nestanka cigareta i pada razine nikotina pojavljuju se neugodni apstinencijski simptomi poput žudnje za cigaretom, razdražljivosti, osjećaja frustracije ili ljutnje, anksioznosti, poteškoća koncentracije, umora, povećanog teka, usporenog rada srca i drugi, koji se povlače čim pušač ponovno zapali cigaretu i namiri potrebu za nikotinom. Stoga nije neobično to što su recidivi kod većine pušača uobičajeni i što su na neki način normalan dio procesa prestanka pušenja. Pušač koji puši kutiju cigareta na dan svakoga dana, sto šezdeset puta udahne nikotin (pri pušenju jedne cigarete duhanski dim se inhalira oko osam puta), odnosno na godinu 57.400 puta podupire i učvršćuje svoju ovisnost o nikotinu.

Na Klinici za neurologiju KB «Sestre milosrdnice» primjenjuje se, u skladu s preporukama SZO, tzv. kratka intervencija i organiziraju se specijalni programi za pušače s visokim stupnjem ovisnosti kojima kratka liječnička intervencija nije dovoljna. Program odvikavanja od pušenja temelji se na načelima *"Breathe free plan to stop smoking"* američkih autora Folkenberga i Mc Farlanda. Radi se o psihoterapijsko-edukacijskom modelu. Kod nekih pušača smo za ublažavanje apstinencijskih simptoma rabili ***nikotinsku zamjensku terapiju***, najčešće u obliku flastera. Razina nikotina u krvi kod primjene nikotinskih flastera je niža nego pri pušenju cigareta, no još uvijek dovoljno visoka da ublaži ili ukloni nikotinski apstinencijski sindrom i odvikavanje od pušenja učini lakšim. Uz to, uklonjeni su svi drugi štetni sastojci koje pušač unosi uz nikotin pušenjem cigareta. Flasteri se lijepe na intaktnu kožu bez dlačica i svakodnevno se mijenjaju. Na raspolaganju su flasteri s različitom količinom nikotina (2l mg , 14 mg, 7 mg). Kod pušača koji puše preko 20 cigareta na dan primjenjuju se flasteri od 21 mg. Trajanje primjene flastera bilo je različito, najčešće oko tjedan dana. Osim lakše iritacije kože kod nekih pušača, nije bilo drugih izrazitijih nuspojava primjene nikotinskih flastera. Nismo zabilježili nijedan slučaj pogoršanja neurološke simptomatologije tijekom primjene nikotinske zamjenske terapije.

Bupropion (Zyban) kao prvo nenikotinsko pomoćno sredstvo u odvikavanju od pušenja, koji se primjenjuje sam ili u kombinaciji s nikotinskom zamjenskom terapijom od 1997. godine kod nas još, nažalost, nije registriran, no postupak registracije je u tijeku. Prema podacima iz literature uspješno se primjenjuje, naročito kod pušača koji boluju od depresije. Daje ga se jedan do dva tjedna prije planiranog

mg strips are used in smokers having more than 20 cigaretters daily. The length of strip application varied, mostly about a week. Except for mild skin irritation, there no major side effects of nicotine strip application. No case of neurologic symptom exacerbation was observed during the use of nicotine replacement therapy.

Unfortunately, ***bupropion (Zyban)***, the first non-nicotine adjuvant in smoking cessation, which has been used alone or in combination with nicotine replacement therapy since 1997, has not yet been registered in Croatia, however, the process of registration in under way. According to literature data, it has been used with success, especially in smokers suffering from depression. It is administered one to two weeks before the scheduled date of stopping smoking (150 mg tbl) to continue with therapy for at least 4 to 6 weeks of smoking cessation. Bupropion decreases the desire for smoking and mitigates withdrawal symptoms. It is well tolerated. Bupropion is not recommended in patients with epilepsy.

An attractively illustrated handbook entitled "You also can quit smoking", of slightly greater dimensions than a cigarette-pack format, 80 pages, has been issued for those who have decided to quit smoking. It helps a smoker to identify which type of smoker he belongs and and how to turn to a nonsmoker through 15 steps, at a pace that suits him, reading and applying the suggested, simple procedures.

The majority of successful abstinents from smoking had at least two to three serious attempts at quitting smoking before they have reached continuous abstinence. According to studies, the length of previous periods of abstinence is important in predicting continuous, longterm abstinence. Besides inappropriate preparation for the process of cessation, the most common reason for smoking relapse within 2-3 weeks of stopping smoking is the presence of nicotine withdrawal syndrome. After 3-4 months of abstinence, a relapse usually occurs due to an attempt to solve an anxious state or to get free from depressive symptoms. A stressful event may provoke a relapse at any time. The smokers who have followed the "Breathe free plan to stop smoking", where special attention is paid to coping with stressful situations, are more successful in solving daily stresses and will less frequently reach for cigarette again in such a situation. Experience shows that desire for cigarette never lasts for more than three minutes. Therefore, the use of so-called "4 P strategy" is highly efficient.

The WBWW strategy	Wait for a while Breathe deeply	Water (take a glass of) Walk

datuma prestanka pušenja (150 mg tbl) i nastavlja se s terapijom najmanje četiri do šest tjedana nakon prestanka pušenja. Bupropion smanjuje želju za pušenjem i ublažava apstinencijske smetnje. Podnošljivost mu je dobra. Kod bolesnika s epilepsijom se ne preporuča uzimanje bupropiona.

Za pušače koji su odlučili prestati pušiti tiskan je odgovarajući, zgodno ilustriran priručnik dimenzija nešto većih od kutije cigareta, od osamdeset stranica, pod naslovom ***"I Vi možete prestati pušiti"***, pomoću kojega svaki pušač može identificirati kojem tipu pušača pripada i u petnaest koraka, tempom koji njemu odgovara, čitajući i primjenjujući predložene jednostavne postupke, postati nepušač.

Većina uspješnih apstinenata od pušenja imala su prije stalne apstinencije najmanje dva do tri ozbiljna pokušaja prestanka pušenja. Prema provedenim ispitivanjima dužina trajanja prethodnih razdoblja apstinencije je važan predskazatelj za stalnu dugotrajnu apstinenciju. Razlog za recidiv pušenja unutar dva do tri tjedna od prestanka pušenja je najčešće, uz neodgovarajuću pripremu za proces prestanka, prisutnost nikotinskog apstinencijskog sindroma. Nakon tri do četiri mjeseca apstinencije recidiv nastaje obično zbog pokušaja da se cigaretom riješi anksiozno stanje ili oslobodi depresivnih simptoma. U bilo koje doba recidiv se može dogoditi zbog stresogenog događaja. Pušači koji su prošli kroz *"Breathe free plan to stop smoking"*, u kojem se posebna pozornost posvećuje suočavanju sa stresogenim situacijama, uspješniji su u rješavanju svakodnevnih stresova i rjeđe im se događa da u stresnoj situaciji ponovno zapale cigaretu. Iskustvo je pokazalo da žudnja za cigaretom nikad ne traje duže od tri minute. Stoga je primjena tzv. "strategije 4 P" vrlo djelotvorna.

Strategija 4 P:	Pričekaj Počni duboko disati	Popij čašu vode Prošeći

Tijekom programa odvikavanja od pušenja pušače se podučava i o načelima zdrave prehrane kako ne bi nakon prestanka pušenja zbog suvišnih kilograma ponovno propušili. Ima više razloga za moguće debljanje nakon prestanka pušenja. Metabolizam se vraća na normalu, oporavlja se osjet okusa i mirisa pa hrana bolje prija, a neki bivši pušači kojima nedostaje cigareta posežu često za slatkišima i drugom visokokaloričnom hranom. Stoga se preporuča piti dosta vode (6-8 čaša na dan), unos vlaknatih tvari (žitarice, voće, povrće), ustati od stola nakon obroka, jesti polagano i to tri uobičajena uravnotežena obroka, unijeti u organizam dosta vitamina (pušenjem se uništavaju vitamini A i C), birati nemasno meso, prednost dati ribi, piti niskokalorična pića, izbjegavati alkohol i redovito vježbati.

During the smoking cessation program, smokers are also education on dietary principles, so as not to restart smoking due to wait gain associated with quitting smoking. There are a number of reasons for the possible weight gain upon stopping smoking. The metabolism returns to normal, the smell and taste recover and the food tastes better; the more so, some former smokers missing their cigarettes may frequently reach for sweets and other high-calorie food. Therefore, water should be taken in abundance (6-8 glasses a day), along with fibrous food (cereals, fruit and vegetables), leaving table after having a meal, eating slowly with the intake properly distributed to the three main meals, taking adequate vitamins (vitamins A and C are destroyed by smoking), lean meat, giving preference to fish, drinking low-calorie drinks, avoiding alcohol, and regular exercise.

Smokers with high-grade dependence having more than 25 cigarettes daily, with many previous attempts at quitting smoking and short periods of abstinence of less than one week, with low education level, poor socioeconomic status, who have not received proper support from the family or live with smokers, who suffer from some psychiatric disorder, and are below age 45 belong to a category characterized by more frequent relapses and greater difficulties in establishing continuous abstinence.

An insight into the high risk emotions and situations that may provoke the subject to reach for cigarette again is important to maintain abstinence. These include irritability, anxiety, anger, boredom, depression, feeling of guilt, presence of some persons, while driving, after meal, during break at the workplace, after work hours, the beginning and the end of the day. These emotions and situations, which are normal part of daily living, in smokers act as "triggers" to have a smoke. Therefore, one should be prepared and find an alternative for any risk situation. One should ask himself: "What could I do instead of having a smoke?" Some tempting situations can be avoided. The ABLE acronym is easy to remember.

A nger	L oneliness
B urden	E mpty stomach

Anger, burden and fatigue, loneliness and boredom, and empty stomach giving a feeling of hunger are frequent "triggers" for smoking. Therefore it is important to learn during the process of smoking cessation how to cope with negative emotions without cigarette.

The smokers who had an opportunity to receive appropriate professional help during the process of smoking cessation continue to live reinforcing the new, healthy

Pušači koji imaju visok stupanj ovisnosti, koji puše preko 25 cigareta na dan, koji imaju iza sebe puno pokušaja prestanka pušenja s kratkim razdobljima apstinencije manjim od tjedan dana, koji imaju nižu naobrazbu, koji imaju slabiji socioekonomski status, koji nemaju odgovarajuću potporu obitelji ili žive s pušačima, koji boluju od neke psihijatrijske bolesti i koji su mlađi od 45 godina spadaju u kategoriju onih koji češće recidiviraju i teže uspostavljaju trajnu apstinenciju.

Za održavanje apstinencije važno je imati uvid u visokorizične emocije i situacije koje mogu navesti osobu da opet zapali cigaretu. To su razdražljivost, tjeskoba, ljutnja, dosada, depresija, osjećaj krivnje, u društvu nekih osoba, tijekom vožnje, poslije obroka, tijekom stanke na poslu, nakon završetka posla, na početku i na kraju dana. Ove emocije i situacije koje su normalan dio svakodnevnog života kod pušača postaju "pokretači" za paljenje cigarete. Zbog toga se treba pripremiti i naći alternativu za svaku rizičnu situaciju.Treba se pitati: "Što mogu učiniti umjesto da zapalim cigaretu?" Neke situacije kušnje mogu se izbjeći. Lagani za upamtiti je akronim STOP:

S rdžba	O samljenost
T eret	P razan želudac

Srdžba, tereti i umor, osamljenost i dosada, te prazan želudac koji daje osjećaj gladi česti su "pokretači" za pušenje. Zbog toga je važno tijekom procesa odvikavanja od pušenja naučiti kako se suočiti s negativnim emocijama bez cigarete.

Pušači koji su imali prilike dobiti odgovarajuću stručnu pomoć tijekom procesa odvikavanja od pušenja nastavljaju živjeti učvršćujući nove zdrave navike koje uz uklanjanje pušenja kao jednog od najubojitijih rizičnih čimbenika ubrzavaju oporavak i smanjuju mogućnost recidiva cerebrovaskularnih bolesti.

Zaključak

Ovisnost o nikotinu je najrasprostranjenija ovisnost diljem svijeta i prema podacima SZO još uvijek jedan od bitnih preventabilnih rizičnih čimbenika za razvoj vaskularnih i malignih bolesti. Cerebrovaskularne bolesti su uz kardiovaskularne i maligne bolesti visoko na ljestvici pobola i smrtnosti u cijelom svijetu. Rizičnim čimbenicima za razvoj ovih bolesti posvećuje se posebna pozornost kako bi se one rizične čimbenike koji se mogu spriječiti uklonilo, a one koji to nisu stavilo pod kontrolu. Pušenje je vrlo ozbiljan preventabilni rizični čimbenik za razvoj vaskularnih bolesti, jer dovodi do povišenja krvnog tlaka, ubrzanog rada srca, sužavanja perifernih krvnih žila, povećanja adhezivnos-

habits which, along with the elimination of smoking as one of the most detrimental risk factors, accelerate recovery and reduce the possibility of cerebrovascular disease recurrence.

Conclusion

Nicotine dependence is the most widely spread addiction worldwide and according to WHO data still one of the substantial preventable risk factors for the development of vascular and malignant diseases. In addition to cardiovascular and malignant diseases, cerebrovascular diseases rank high on the morbidity and mortality scale all over the world. Risk factors for these diseases are paid special attention in order to eliminate the preventable ones and to control the others that cannot be influenced upon. Smoking is a very serious preventable risk factor for the development of vascular diseases, because elevates blood pressure, accelerates heart rate, narrows blood vessels, increases platelet adhesion and aggregation, increased plasma fibrinogen and blood carboxyhemoglobin, decreases angioprotective HDL and increases LDL, total cholesterol and free fatty acids. Smokers have a higher prevalence ischemic stroke and subarachnoidal hemorrhage, whereas carotid CDFI and TCD more frequently reveal pathologic changes.

In spite of the programs for tobacco use reduction, every eight minutes somebody dies in the world from the consequences of smoking, so that smoking is responsible for more than 4 million deaths *per* year. It is estimated that in Croatia, 14,000 persons die due to the consequences of smoking *per* year.

Each smoker is sooner or later challenged with quitting smoking. Most of them decide on stopping smoking because of some health problem. As a large proportion of smokers cannot establish and maintain abstinence from smoking without proper support and professional assistance, all those who want it should be provided appropriate help, i.e. smoking cessation programs should be integrated in regular therapeutic procedures in both hospital and outpatient institutions. Each physician should provide the patient, in direct contact, with due information on health hazards associated with smoking; this information should be individualized, i.e. related to the patient's complaints, rather than general. It should emphasize that, in addition to the physician's support and assistance, the same from the family, friends and colleagues is of utmost importance for abstinence maintenance. The patient's family members should be informed about the main characteristi i agregacije trombocita, porasta fibrinogena u plazmi, povećanja razine karboksihemoglobina u krvi, pada razine angioprotektivnog HDL i povećanja razine LDL, povišenja ukupnog kolesterola, te povišenja razine slobodnih masnih kiselina. Pušači češće obolijevaju od ishemijskog moždanog udara i subarahnoidnog krvarenja, a na CDFI karotida i TCD češće se zapažaju patološke promjene. Unatoč programima suzbijanja pušenja duhana, na razini svijeta svakih osam minuta netko umre zbog posljedica pušenja pa je tako pušenje odgovorno za preko četiri milijuna smrti na godinu. Procjenjuje se da u Hrvatskoj na godinu umre 14.000 osoba zbog posljedica pušenja.

Svaki pušač se kad-tad nađe pred izazovom prestanka pušenja. Većina pušača donosi odluku o prestanku pušenja potaknuta zdravstvenim problemima. Kako velik broj pušača nije u stanju bez potpore i stručne pomoći usposta-viti i održati apstinenciju od pušenja, neophodno je osigurati svima koji to žele odgovarajuću pomoć, odnosno programe odvikavanja od pušenja uklopiti u redovite terapijske postupke u bolničkim i izvanbolničkim ustanovama. Svaki liječnik pozvan je da u izravnom kontaktu pruži svom bolesniku informaciju o oštećenjima zdravlja nastalim zbog pušenja, koja mora biti što osobnija, odnosno povezana s poteškoćama koje bolesnik navodi, a ne općenita. Uza stručnu liječničku potporu i pomoć treba istaknuti kako je za održavanje apstinencije bitna potpora i razumijevanje obitelji, prijatelja i kolega na radnom mjestu. Obitelj bolesnika mora biti upoznata s osnovnim značajkama ovisnosti o nikotinu, s načelom "sve ili ništa", kao i s opasnostima pasivnog pušenja. U domu i na radnom mjestu bitno je spriječiti izloženost pasivnom pušenju, odnosno osigurati nepušačko ozračje.

Nepušačko ozračje na radnom mjestu osigurava i Zakon o ograničenoj uporabi duhana i duhanskih proizvoda koji je 1999. g. izglasan u Hrvatskom saboru. Poštivanjem spomenutog zakona ne samo da se štiti nepušače, već se bolesnicima, bivšim pušačima pomaže da se brže oporave i održe apstinenciju koja je bitna za očuvanje zdravlja i sprječavanje recidiva cerebrovaskularnih i tridesetak drugih bolesti povezanih s aktivnim i pasivnim pušenjem.

tics of nicotine dependence, the "all or none" principle, and the risks of passive smoking. It is of great importance to prevent exposure to passive smoking, i.e. to ensure nonsmoking setting both at home and at work place.

Nonsmoking setting at work place is regulated by the Act on Restricted Use of Tobacco and Tobacco Products, enacted by the Croatian Parliament in 1999. Following this Act provisions does not only protect nonsmokers but also assists patients, former smokers to recover earlier and maintain abstinence, which is substantial for health protection and to prevent recurrence of cerebrovascular disease and some thirty other diseases known to be associated with active and passive smoking.

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TEAM APPROACH IN PROVIDING CARE FOR STROKE PATIENTS
TIMSKI PRISTUP U ZBRINJAVANJU BOLESNIKA S MOŽDANIM UDAROM

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Owing to great advances in medicine, living to one's 100th is no more 'science fiction' today, while the quality of living to an advanced age has become more important than the mere age. Achievements in biomedical sciences provide ever more support to our hope that various age related damages could be reduced and even many degenerative symptoms characteristic of old age avoided. To make this endpoint real, we need to assist the nature and adopt as early as possible such a lifestyle that not only averts premature death but also helps live to a green old age in good health, pleasure and shape. Healthy brain and vascular system are one of the main preconditions for body and soul harmony. Vascular diseases are enemy No. 1 of the modern human, and the most common cause of death and permanent disability. Atherosclerosis is the most common vascular disease.

The term cerebrovascular diseases refers to vascular diseases associated with more or less pronounced neurologic events, and almost always with mental derangement. Stroke is the final stage of the classic form of cerebrovascular disease. All stroke types are directly or indirectly related to vascular disease, i.e. to atherosclerotic lesions of blood vessels. Stroke remains the leading cause of disability and third most common cause of mortality, immediately following cardiovascular diseases and malignant diseases.

In western countries, especially in the USA, the number of stroke patients has been on a decrease in recent years, primarily due to organized preventive actions and adoption of a healthy lifestyle. In Croatia, unfortunately, no such favorable trends have yet been observed, and stroke remains quite a common disease. The fact that stroke ever more frequently occurs in ever younger age groups, with as many as 45% of stroke cases being recorded in the 46-59 age group, it has become a serious concern.

Likewise other degenerative diseases, atherosclerosis develops over years. The factors contributing to the development of atherosclerosis can be divided as follows:

Danas, zahvaljujući napretku medicine, doživjeti stotu godinu više nije znanstvena fantastika, a kvaliteta doživljenih godina važnija je od njihovog broja. Dostignuća biomedicinske znanosti sve više potkrepljuju nadu da možemo smanjiti oštećenja u starosti i čak izbjeći mnoge degenerativne simptome ovog životnog razdoblja. Kako bismo to postigli sami moramo pomoći prirodi i usvojiti što prije način života koji ne samo da otklanja preranu smrt, već pomaže da se i visoke godine prožive u zdravlju, sreći i dobroj kondiciji. A za postizanje sklada duha i tijela zdrav mozak i žile jedan su od osnovnih preduvjeta. Bolesti krvnih žila neprijatelj su broj 1 suvremenog čovjeka i najčešći uzrok smrti i trajne invalidnosti. Najčešća bolest krvnih žila je ateroskleroza.

Pod pojmom cerebrovaskularih bolesti podrazumijevaju se bolesti krvnih žila s manje ili više izraženim neurološkim ispadima i gotovo uvijek s psihičkim promjenama. Zadnji stadij klasičnog oblika cerebrovaskularne bolesti je mo-žđani udar. Sve vrste moždanih udara su izravno ili neizravno povezane s bolestima krvnih žila, odnosno s aterosklerotskim promjenama na krvnim žilama. Moždani udar je još uvijek vodeći uzrok invalidnosti, te treći po učestalosti uzorak smrtnosti, odmah nakon kardiovaskularnih i zloćudnih bolesti.

U zapadnim zemljama, osobito u SAD, broj oboljelih od moždanog udara posljednjih godina se smanjuje, u prvom redu zahvaljujući organiziranim preventivnim akcijama i usvajanju zdravog načina života. Nažalost, u našoj zemlji ne uočavaju se ovakvi povoljni trendovi te se moždani udar još uvijek javlja vrlo često. Osobito je zabrinjavajuće to što se moždani udar sve češće javlja u sve mlađim dobnim skupinama, tako da se čak oko 45% moždanih udara javlja u dobnoj skupini od 46. do 59. godine života.

Ateroskleroza se, poput drugih degenerativnih bole.sti, razvija godinama. Činitelji koji doprinose razvitku ateroskleroze mogu se podijeliti na one:

– nonmodifiable factors: age, sex, genetic heritage;
– modifiable factors: arterial hypertension, hyperlipoproteinemia, diabetes mellitus, cardiac diseases, coagulation disorders, elevated level of uric acid, oral contraceptives, elevated level of homocysteine; and
– removable factors: smoking, alcoholism, stress, overweight, lack of exercise.

Prevention remains the most efficient and most important way to influence vascular diseases including stroke. The nurse as well as other health professionals need to identify and consider all risk factors present in each individual patient. Within the primary prevention measures, the nurse will detect the risk factors for stroke and advise the patient to eliminate those that can be removed (smoking, alcohol abuse, lack of physical activity, obesity, etc.), thus promoting healthy habits and healthier lifestyle (nonsmoking, nondrinking, physical activity, etc.).

Considering the risk factors that cannot be modified, the nurse will take care for these to be kept within acceptable limits (due control of arterial blood pressure, blood glucose, blood lipids and uric acid, regular visits and control examinations at outpatient specialist clinics). Patients with multiple risk factors are at a much higher risk of stroke than those with a single risk factor. In these patients, every effort should be made to remove all modifiable risk factors (in the above example, the patient should quit smoking). This can result in a considerable decrease in the prevalence of both stroke and other vascular diseases.

Some patients will sustain a stroke in spite of taking all preventive actions. On delivering care to stroke patients, the nurse is a relatively independent creative-innovative health care provider, which primarily refers to patient care by either organizing or providing it. The nurse follows up the stroke patient from the emergency neurology clinic through stroke unit or neurology intensive care unit to rehabilitation facility. Thus, the nurse is included in all steps of stroke patient care, from admission through acute management, subacute management and early rehabilitation to late rehabilitation at inpatient facilities. The more so, the nurse's engagement extends beyond the patient's discharge from the hospital for home care, as she identifies and takes care of all risk factors present in each individual patient as part of secondary prevention. Secondary prevention also includes providing education to the patient and his family members on therapy and on the need of appropriate rehabilitation.

Through the domiciliary care system, the nurse educates patients with a history of stroke and their family members on how to live well with the residual neurologic

– na koje se ne može utjecati: dob, spol, genetsko nasljeđe,
– na koje se može utjecati: arterijska hipertenzija, hiperlipoproteinemija, šećerna bolest, razne srčane bolesti, poremećaji zgrušavanja krvi, povišena količina mokraćne kiseline, uzimanje oralnih kontraceptiva, povišena razina homocisteina,
– koji su otklonjivi: pušenje, alkoholizam, stres, prekomjerna tjelesna težina, nedovoljna tjelesna aktivnost.

Prevencija je još uvijek najučinkovitiji i najznačajniji način na koji se može djelovati na bolesti krvnih žila, pa tako i na moždani udar. Medicinska sestra, kao i ostali zdravstveni djelatnici, treba identificirati sve rizične čimbenike prisutne kod svakog pojedinog bolesnika i voditi brigu o njima. Medicinska sestra u okviru primarne prevencije otkriva rizične čimbenike za nastanak moždanog udara, te utječe na bolesnika da se otklone čimbenici rizika za koje je to moguće (pušenje, prekomjerno pijenje alkohola, tjelesna neaktivnost, pretilost itd.). Na taj način ona promiče zdrave navike i zdraviji način života (nepušenje, nepijenje, tjelesna aktivnost itd.). Za ostale čimbenike rizika (na koje se može utjecati) brine se da ih bolesnik održava pod kontrolom u prihvatljivim granicama (regulacija arterijskog tlaka, regulacija šećera, masnoća, mokraćne kiseline u krvi, redoviti pregledi i kontrole u specijalističkim ambulantama). Bolesnici s više čimbenika rizika su mnogostruko skloniji obolijevanju od moždanog udara od bolesnika kod kojih je prisutan samo jedan čimbenik rizika. Kod takvih bolesnika potrebno je učiniti sve da se uklone svi uklonjivi čimbenici rizika (u gore navedenom primjeru da bolesnik prestane pušiti). Time se može postići značajno smanjenje učestalosti kako moždanog udara tako i ostalih krvožilnih bolesti.

Usprkos i najbolje provedenim preventivnim akcijama neki bolesnici će dobiti moždani udar. U zbrinjavanju oboljelih od moždanog udara medicinska sestra je relativno samostalan kreativno-inovacijski nositelj zdravstvene njege, što se ponajprije odnosi na skrb o bolesniku, bilo da sestra organizira ili provodi tu skrb. Medicinska sestra prati bolesnika s moždanim udarom od hitne neurološke ambulante preko jedinica za moždani udar ili odjela intenzivne skrbi, neuroloških odjela pa sve do rehabilitacijskih odjela. Sestra je, dakle, uključena u sve faze zbrinjavanja bolesnika s moždanim udarom od prijma preko akutnog zbrinjavanja, subakutnog zbrinjavanja, započinjanja rane rehabilitacije pa sve do kasnije rehabilitacije u stacionarnim ustanovama. No, s otpuštanjem bolesnika nakon rehabilitacije u stacionarnim ustanovama ne prestaje angažiranje medicinske sestre. U okviru sekundarne prevencije me-

deficit. The nurse ensures the most successful rehabilitation of stroke patients and their resuming the usual daily activities to the highest possible level. Through education, stroke patients and their families accept the sequels of stroke, while the nurse helps them facilitate their daily living with various forms of neurologic deficit.

The nurse has a prominent role also in education of the population at large about the signs and symptoms of stroke, in order to increase the public awareness of stroke and its causes, ways to avoid its occurrence, advantages of a healthy lifestyle, stroke sequels and living with them. The fatalist concept of stroke and the nihilist approach to stroke therapy, that are still widely present in our society, will thus gradually change.

Accordingly, the nurse is an independent, creative-innovative care provider for stroke patients, plays a very important role in all aspects of stroke care (from prevention through rehabilitation to domiciliary care and home care), and is a crucial member of the team managing stroke patients.

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dicinska sestra identificira sve rizične čimbenike prisutne kod svakog pojedinog bolesnika i vodi brigu o njima. Obrazuje bolesnika i članove njegove obitelji o terapiji u okviru sekundarne prevencije i o potrebi rehabilitacije bolesnika.

Kroz patronažnu službu medicinska sestra obrazuje bolesnike s preboljelim moždanim udarom i članove njihovih obitelji o tome kako što kvalitetnije živjeti sa zaostalim neurološkim deficitom. Sestra omogućava što uspješniju rehabilitaciju i uključivanje u život bolesnika s preboljelim moždanim udarom. Bolesnici i članovi njihovi obitelji kroz izobrazbu prihvaćaju posljedice moždanog udara, a sestra im pomaže u olakšavanju života s raznim oblicima neuroloških deficita.

Vrlo je važna uloga medicinske sestre i u izobrazbi šireg pučanstva o simptomima i znacima moždanog udara, kako bi se podigla svjesnost populacije o moždanom udaru, kao i o njegovim uzrocima, načinima na koje se može izbjeći moždani udar, o prednostima zdravog načina života, o posljedicama moždanog udara i o življenju s posljedicama moždanog udara. Na taj način će se postupno promijeniti još uvijek prisutno fatalističko shvaćanje moždanog udara i nihilistički pristup u terapiji moždanog udara.

Iz svega navedenog može se vidjeti da je medicinska sestra u zbrinjavanju oboljelih od moždanog udara relativno samostalan kreativno-inovativni nositelj zdravstvene njege i skrbi o bolesniku, te da je uloga medicinske sestre u svim oblicima zbrinjavanja bolesnika s moždanim udarom (od prevencije preko rehabilitacije do patronaže i kućne njege) vrlo značajna i da je medicinska sestra bitan član tima koji sudjeluje u zbrinjavanju bolesnika s moždanim udarom.